

Wong, K.
280187

=> fil reg; s (noribogaine? or ibogaine?)/cn
FILE 'REGISTRY' ENTERED AT 10:44:55 ON 30 SEP 94
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L1 1 NORIBOGAINE?/CN
29 IBOGAINE?/CN
29 (NORIBOGAINE? OR IBOGAINE?)/CN

=> fil ca; s l1 or (noribogain? or ibogain? or alkaloid? or (tabernanth?
or t)(w)iboga or 12(w)(methoxyibogamin? or methoxy ibogamin?))/ab,bi
FILE 'CA' ENTERED AT 10:46:23 ON 30 SEP 94
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FILE COVERS 1967 - 17 Sep 1994 (940917/ED) VOL 121 ISS 12

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THE BASIC INDEX NOW INCLUDES ABSTRACT TEXT. SEE NEWS FOR DETAILS.

122 L1
0 NORIBOGAIN?/AB
0 NORIBOGAIN?/BI
89 IBOGAINE?/AB
106 IBOGAINE?/BI
22596 ALKALOID?/AB
38087 ALKALOID?/BI
30 TABERNANTH?/AB
39 TABERNANTH?/BI
286917 T/AB
307567 T/BI
81 IBOGA/AB
126 IBOGA/BI
14 (TABERNANTH? OR T)(W)IBOGA
525262 12/AB
561652 12/BI
1 METHOXYIBOGAMIN?/AB
2 METHOXYIBOGAMIN?/BI
24 METHOXY/AB
62 IBOGAMIN?/AB

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0 METHOXY IBOGAMIN?/AB
  ((METHOXY(W)IBOGAMIN?)/AB)
41 METHOXY/BI
116 IBOGAMIN?/BI
0 METHOXY IBOGAMIN?/BI
  ((METHOXY(W)IBOGAMIN?)/BI)
1 12(W) (METHOXYIBOGAMIN? OR METHOXY IBOGAMIN?)
38148 L1 OR (NORIBOGAIN? OR IBOGAIN? OR ALKALOID? OR (TABERNANTH
? OR T) (W)IBOGA OR 12(W) (METHOXYIBOGAMIN? OR METHOXY IBOG
AMIN?)/AB, BI
L2
=> s. (12(w)(methoxyibogamin? or methoxy ibogamin?))/ab,bi
525262 12/AB
561652 12/BI
1 METHOXYIBOGAMIN?/AB
2 METHOXYIBOGAMIN?/BI
27052 METHOXY/AB
62 IBOGAMIN?/AB
0 METHOXY IBOGAMIN?/AB
  ((METHOXY(W)IBOGAMIN?)/AB)
44034 METHOXY/BI
116 IBOGAMIN?/BI
0 METHOXY IBOGAMIN?/BI
  ((METHOXY(W)IBOGAMIN?)/BI)
L3 1 (12(W) (METHOXYIBOGAMIN? OR METHOXY IBOGAMIN?))/AB, BI
=> s 12 or 13
L4 38148 L2 OR L3
=> s 14 and (treat? or therap?)/ab,bi
1203682 TREAT?/AB
1407163 TREAT?/BI
65305 THERAP?/AB
89084 THERAP?/BI
L5 4631 L4 AND (TREAT? OR THERAP?)/AB, BI
=> s 15 and (depend? or withdraw? or crav? or abus?)/ab,bi
940229 DEPEND?/AB
1019562 DEPEND?/BI
28899 WITHDRAW?/AB
29868 WITHDRAW?/BI
182 CRAV?/AB
206 CRAV?/BI
2693 ABUS?/AB
3805 ABUS?/BI
L6 294 L5 AND (DEPEND? OR WITHDRAW? OR CRAV? OR ABUS?)/AB, BI
=> s 16 and (substanc? or drug# or alcohol? or narcotic? or drink?)/ab,bi
153213 SUBSTANC?/AB
329316 SUBSTANC?/BI
193335 DRUG#/AB
267746 DRUG#/BI
8063 ALCOHOL?/AB

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137170 ALCOHOL?/BI
3068 NARCOTIC?/AB
6223 NARCOTIC?/BI
26255 DRINK?/AB
32454 DRINK?/BI
102 L6 AND (SUBSTANC? OR DRUG# OR ALCOHOL? OR NARCOTIC? OR DRI
NK?)/AB,BI

L7

=> s l6 and chemical?/ab,bi
4332 CHEMICAL?/AB
584135 CHEMICAL?/BI

L8 8 L6 AND CHEMICAL?/AB,BI

=> s l5 and ((substanc? or drug# or alcohol? or narcotic? or drink? or
chemical?)(w)(depend? or withdraw? or crav? or abus?))/ab,bi

153213 SUBSTANC?/AB
329316 SUBSTANC?/BI
193335 DRUG#/AB
267746 DRUG#/BI
8063 ALCOHOL?/AB
137170 ALCOHOL?/BI
3068 NARCOTIC?/AB
6223 NARCOTIC?/BI
26255 DRINK?/AB
32454 DRINK?/BI
4332 CHEMICAL?/AB
584135 CHEMICAL?/BI
940229 DEPEND?/AB
1019562 DEPEND?/BI
28899 WITHDRAW?/AB
29868 WITHDRAW?/BI
182 CRAV?/AB
206 CRAV?/BI
2693 ABUS?/AB
3805 ABUS?/BI
5463 ((SUBSTANC? OR DRUG# OR ALCOHOL? OR NARCOTIC? OR DRINK? OR
CHEMICAL?)(w)(DEPEND? OR WITHDRAW? OR CRAV? OR ABUS?))/AB
BI

L9

28 L5 AND ((SUBSTANC? OR DRUG# OR ALCOHOL? OR NARCOTIC? OR DR
INK? OR CHEMICAL?)(w)(DEPEND? OR WITHDRAW? OR CRAV? OR ABU
S?))/AB,BI

=> s l5 and ((substanc? or drug# or alcohol? or narcotic? or drink? or
chemical?)(l)(depend? or withdraw? or crav? or abus?))/ab,bi

153213 SUBSTANC?/AB
329316 SUBSTANC?/BI
193335 DRUG#/AB
267746 DRUG#/BI
8063 ALCOHOL?/AB
137170 ALCOHOL?/BI
3068 NARCOTIC?/AB
6223 NARCOTIC?/BI
26255 DRINK?/AB

32454 DRINK?/BI
 4332 CHEMICAL?/AB
 584135 CHEMICAL?/BI
 940229 DEPEND?/AB
 1019562 DEPEND?/BI
 28899 WITHDRAW?/AB
 29868 WITHDRAW?/BI
 182 CRAV?/AB
 206 CRAV?/BI
 2693 ABUS?/AB
 3805 ABUS?/BI
 55416 ((SUBSTANC? OR DRUG# OR ALCOHOL? OR NARCOTIC? OR DRINK? OR
 CHEMICAL?) (L) (DEPEND? OR WITHDRAW? OR CRAV? OR ABUS?)) /AB
 ,BI
 L10 92 L5 AND ((SUBSTANC? OR DRUG# OR ALCOHOL? OR NARCOTIC? OR DR
 INK? OR CHEMICAL?) (L) (DEPEND? OR WITHDRAW? OR CRAV? OR ABU
 S?)) /AB, BI

=> d l9 1-28 .beverly; fill biosi; s l1 or (noribogain? or ibogain? or
 alkaloid? or (tabernanth? or t)(w)iboga or l2(w)(methoxyibogamin? or
 methoxy ibogamin?))

L9 ANSWER 1 OF 28 CA COPYRIGHT 1994 ACS
 AN 121:141708 CA
 TI Compacted drug body for use in the mechanical generation of
 inhalable active-substance particles
 SO PCT Int. Appl., 20 pp.
 CODEN: PIXXD2
 IN Hugemann, Bernhard; Burgschat, Hans G.; Heide, Helmut; Pabst,
 Joachim
 AI WO 93-EP1158 930511
 PI WO 9414490 A1 940707
 PY 1994
 AB The invention concerns a compacted drug body with an isotropic solid
 structure, the compacted body being produced by isostatic
 compression (50-500 MPa), injection molding, or die casting. The
 drug may be a respiratory therapeutic agent such as a
 .beta.-mimetic, anticholinergic, steroid, allergy inhibitor, or PAF
 antagonist, a peptide hormone, addiction control agent, analgesic,
 alkaloid, etc., combined with an inert carrier. The
 compacted body may be in a container forming part of the cap closure
 of the inhaler.

0 L9 ANSWER 2 OF 28 CA COPYRIGHT 1994 ACS
 AN 121:49988 CA
 TI The putative anti-addictive drug ibogaine is a competitive
 inhibitor of [3H]MK-801 binding to the NMDA receptor complex
 SO Psychopharmacology (Berlin) (1994), 114(4), 672-4
 CODEN: PSCHDL; ISSN: 0033-3158
 AU Popik, Piotr; Layer, Richard T.; Skolnick, Phil
 PY 1994
 AB Ibogaine is a putative anti-addictive drug with potential
 efficacy for the treatment of opiate, stimulant, and alc.

abuse. The authors now report ibogaine is a competitive inhibitor (Ki, 1.01 +- 0.1 .mu.M) of [3H]MK-801 binding to N-methyl-D-aspartate (NMDA) receptor coupled cation channels. Since MK-801 can attenuate the development of tolerance to morphine and alc. as well as sensitization to stimulants in preclin. studies, the reported ability of ibogaine to modify drug-seeking behavior in man may be attributable to a blockade of NMDA receptor coupled cation channels.

✓L9 ANSWER 3 OF 28 CA COPYRIGHT 1994 ACS
AN 121:923 CA

TI Aconitane and tetrahydroprotaberine derivatives for treatment of drug withdrawal syndrome
SO Brit. UK Pat. Appl., 35 pp.
CODEN: BAXXDU

IN Qu, Yueqian; Qu, Peng; Qu, Ming
AI GB 93-19500 930921
PI GB 2271059 A1 940406
PY 1994

AB Aconitane derivs. and their inorg. acid salts or their mixt., or tetrahydroprotaberine derivs. (Markush structures given) with or without anticholinergic agents are used for treatment of drug withdrawal syndrome. Mice were injected s.c. either with 80mg morphine.HCl (I) /kg or 8mg lappaconitine.HBr (II) /kg daily for 20 days. All the mice were given i.p. injection of 10mg allyl dromaran/kg 6 h after the last dose and then placed in a cage. Mice receiving I looked excited, frequently run around and showed pilo-erection reaction; while mice receiving II looked quiet and immobile and showed no pilo-erection reaction.

✓L9 ANSWER 4 OF 28 CA COPYRIGHT 1994 ACS
AN 121:871 CA

TI Methods for identifying and using low/non-addictive opioid analgesics
SO PCT Int. Appl., 72 pp.
CODEN: PIXXD2

IN Qin, Boyi; Shen, Kefei; Gong, Xiongqi; Crain, Stanley M.; Mao, Huang; Wang, Chang Yi
AI WO 93-US8869 930917
PI WO 9406426 A1 940331
PY 1994

AB The present invention relates to a method of using a bioassay consisting of an electrophysiol. method and a cell culture system of dorsal root ganglion (DRG) neurons to screen and identify opioids with a high potential for use as "low- or non-addictive" analgesics. Another aspect of the invention relates to a specific group of opioid alkaloids and analogs thereof identified by the bioassay of the invention for the unique ability to activate only inhibitory, but not excitatory, opioid receptor function, for use as low- or non-addictive analgesics and for the treatment of opioid addiction. The present invention also relates to the prepn. of dihydroetorphine hydrochloride (7.alpha.[1-(R)-hydroxy-1-methylbutyl]-6,14-endo-ethanotetrahydrooripavine hydrochloride)

(I-HCl) and a pharmaceutical compn. comprising the compd. as an active ingredient in the form of a pharmaceutically acceptable salt. The selective inhibitory but not excitatory effect of etorphine and I on the action potential duration of sensory DRG neurons in culture is described, as are the anti-addictive effects of I treatment in animal and clin. studies. I elicited potent low- or nonaddictive analgesia in patients with acute and chronic pain. The analgesic effect of various I salts was detd. Injectable and sublingual tablet formulations of I-HCl are included.

✓L9 AN
TI
SO
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ANSWER 5 OF 28 CA COPYRIGHT 1994 ACS
120:291955 CA
Aconitane derivatives used as a medication to treat addiction
U.S., 12 pp.
CODEN: USXXAM
Qu, Yueqian; Qu, Peng
US 92-912791 920713
PI US 5290784 A 940301
PY 1994

A medication is disclosed for treatment of individuals who are addicted to drugs or narcotics (opium, morphine, heroin, cocaine, marijuana, amphetamines, etc.), as are preparative methodol. for the medication and a treatment method using the medication. The medication is an aconitane deriv. I(R = .alpha.-OMe, .beta.-OMe, .alpha.-OH; R1 = OAcABz, OH, OABz, H; R2-R5 = H, OH; R6 = OMe, OBz, OAc, OH) or II (R1 = R2 = R3 = OH). The medication has no drug-dependence, a high cure effect, fast action, and low side effects. Treatment of heroin addicts and opium addicts with e.g. lappaconitine-HBr is described.

✓L9 AN
TI
SO
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AB

ANSWER 6 OF 28 CA COPYRIGHT 1994 ACS
120:270449 CA
Anticonvulsant substituted quinazolones
U.S., 7 pp. Cont. of U.S. Ser. No. 651,436, abandoned.
CODEN: USXXAM
Dwivedi, Chandradhar; Omodt, Gary W.
US 92-947985 920921
PI US 5283247 A 940201
PY 1994

A process for the prepn. of substituted quinazolones represented by the formula I: wherein X1 is N, S, O, or CH, X2 is N or CH, R1 and R2 are H, NO2, or NH2 except that when one of R1 and R2 is NO2 or NH2 the other is H, R3 and R4 are alkyl with 1-5 C atoms, and R5, R6, and R7 are H or halogen, provided that when X1 is N, S, or O, X2 is CH comprises treatment of primary amine with anthranil under a low flame. Quinolones I and their N1-oxide derivs. and methods of using them to treat or prevent convulsions in mammals are reported.

✓L9 AN
AN

ANSWER 7 OF 28 CA COPYRIGHT 1994 ACS
120:154169 CA

✓ TI

Antagonists at excitatory opioid receptors on sensory neurons in culture increase potency and specificity of opiate analgesics and attenuate development of tolerance/dependence

SO

Brain Res. (1994), 636(2), 286-97

AU

CODEN: BRREAP; ISSN: 0006-8993

PY

Shen, Ke-Fei; Crain, Stanley M.

AB

1994

At low (< nM) concns., .mu., .delta. or .kappa. opioid peptides as well as morphine and other opioid alkaloids elicit dose-dependent excitatory prolongation of the calcium-dependent component of the action potential duration (APD) of many mouse sensory dorsal root ganglion (DRG) neurons, whereas application of the same opioids at higher (uM) concns. results in inhibitory shortening of the APD. These bimodal opioid excitatory/inhibitory effects on DRG neurons are blocked by naloxone. In contrast to bimodally acting opioids, the opioid alkaloids, etorphine and dihydroetorphine (thebaine-orphavine derivs.), uniquely elicited only dose-dependent, naloxone-reversible inhibitory effects on sensory neurons in DRG-spinal cord explants, even at concns. as low as 1 pM, and showed no excitatory effects at lower concns. These remarkably potent inhibitory opioid receptor agonists also act as antagonists at excitatory opioid receptors since pretreatment of DRG neurons with subthreshold concns. (< pM) blocked excitatory APD prolongation by nM morphine (or other opioids) and unmasked inhibitory APD shortening which generally requires much higher concns. Furthermore, acute application of pM-nM etorphine to chronic .mu.M morphine- or [D-Ala2,D-Leu5]enkephalin (DADLE)-treated DRG neurons blocked the nM naloxone-pptd. APD prolongation that generally occurs in DRG cells sensitized by bimodally acting opioids. In the presence of pM etorphine, chronic treatment of DRG neurons with .mu.M morphine or DADLE no longer resulted in development of tolerance/dependence effects, as previously obsd. after similar chronic opioid treatment in the presence of cholera toxin-B subunit. These in vitro studies may clarify the mechanisms underlying the potent analgesic effects of etorphine and dihydroetorphine in vivo and to guide the use of these and other excitatory opioid receptor antagonists in attenuating development of opiate dependence/addiction.

✓ L9

ANSWER 8 OF 28 CA COPYRIGHT 1994 ACS

AN

120:153743 CA

TI

Des-Tyrosyl dynorphin analogs, and therapeutic uses.

SO

thereof

IN

PCT Int. Appl., 24 pp.

AI

CODEN: PIXXD2

PI

Lee, Nancy M.; Loh, Horace H.; Takemori, Akira E.

PY

WO 93-US5161 930601

AB

WO 9325217 A1 931223

1993

Dynorphin analogs are disclosed which have similar activity to endogenous dynorphin, but are des-Tyr or des-Tyr-Gly with respect to endogenous dynorphin. The peptides have therapeutic uses, e.g. administration to a host tolerant to a narcotic analgesic in

order to potentiate activity of the narcotic analgesic and/or to block withdrawal symptoms. Peptides of the invention were tested in naloxone-challenged morphine-tolerant (addicted) animals; the peptide was administered prior to the naloxone challenge. In animals receiving the peptide [e.g. dynorphin (3-13), which is des-Tyr-Gly] 5 min before naloxone administration, much more naloxone was needed to ppt. the animal into a state of narcotic withdrawal. This means that the peptide caused the addicted animal to be not as dependent on morphine as it would be without such pretreatment.

L9
AN
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AB

ANSWER 9 OF 28 CA COPYRIGHT 1994 ACS
120:69468 CA

Ibogaine reduces preference for cocaine consumption in C57BL/6By mice

Pharmacol., Biochem. Behav. (1994), 47(1), 13-19
CODEN: PBBHAU; ISSN: 0091-3057

Sershen, Henry; Hashim, Audrey; Lajtha, Abel
1994

After a period of forced exposure to 300 mg/L cocaine HCl in drinking water for a period of one week, followed by forced exposure to 200 mg/L cocaine for an addnl. week, male C57BL/6By mice developed a preference for cocaine when given a choice of drinking either water or a soln. contg. cocaine (200 mg/L). The mean daily intake of cocaine during the choice period was 26 ± 1 mg/kg or, when expressed as the ratio of cocaine over total fluid intake, represented a cocaine preference of $71 \pm 2\%$. Administration of ibogaine HCl (40 mg/kg, two injections 6 h apart) two weeks after the beginning of the choice period reduced the cocaine preference for at least five days; the mean daily intake of cocaine was reduced by 38% (to 16 ± 1 mg/kg per day; $p < 0.05$) and cocaine preference was reduced to $41 \pm 2\%$ (cocaine fluid consumption/total fluid intake). An acute challenge injection of cocaine (25 mg/kg SC) produced a significant increase in cocaine-induced locomotor activity and stereotypy in mice previously exposed to cocaine in their drinking water (cocaine choice group). Five days after ibogaine administration, locomotor and stereotypy activity were significantly lower after a challenge injection of cocaine (25 mg/kg SC). Brain levels of cocaine 35 min after the challenge injection of cocaine were approx. 25% higher in ibogaine-treated mice (7.2 ± 0.5 and 9.3 ± 0.8 $\mu\text{g/g}$ wet wt for water vs. mice treated with water plus ibogaine and 9.3 ± 0.2 and 11.8 ± 0.7 $\mu\text{g/g}$ wet wt for cocaine drinking vs. cocaine drinking plus ibogaine treatment). Neither the redn. in cocaine preference nor attenuation in cocaine-induced ambulatory and stereotypy activity by ibogaine was accounted for by changes in brain levels of cocaine.

L9
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ANSWER 10 OF 28 CA COPYRIGHT 1994 ACS
120:69398 CA

Comparison of the behavioral effects of ibogaine from three sources: mediation of discriminative activity

50

Eur. J. Pharmacol. (1993), 249(1), 79-84
 CODEN: EJPHAZ; ISSN: 0014-2999

AU

Schechter, Martin D.; Gordon, Timothy L.

PY

1993

AB

Ibogaine is an alkaloid employed for its hallucinatory properties in West Central Africa and which has been the subject of alleged efficacy as an aid in the interruption and treatment of chem. dependency. The major sources of the Schedule I agent are: Sigma Chem. Co., the National Institute on Drug Abuse and as NDA International Inc.'s Endabuse. The intent of the present study was to train rats to discriminate the interoceptive stimuli produced by (10 mg/kg, i.p. administered) **ibogaine**. Once trained, these rats were used to investigate the dose-response effects to **ibogaine** from each of the 3 suppliers. In addn., stimulus generalization to the dopamine antagonist CGS 10746B, as well as to the serotonergically active compds. fenfluramine, TFMPP, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, MDMA, quipazine and LSD was tested. **Ibogaine** was readily discriminable from its vehicle, and **ibogaine** from each of the 3 suppliers produced statistically similar discrimination, with ED50 values ranging 2.5-3.4 mg/kg. In addn., various doses of the other drugs tested produced, at best, intermediate **ibogaine** -appropriate responding and, thus, no drug tested can be considered to generalize to **ibogaine**-like stimuli. The multiple actions of **ibogaine** that have been cited in the literature are discussed. The similarity in potency of **ibogaine** from 3 potential suppliers should allow for preclin. work using any of these research samples to be comparable.

59

ANSWER 11 OF 28 CA COPYRIGHT 1994 ACS

AN

120:45657 CA

CI

Degeneration of Purkinje cells in parasagittal zones of the cerebellar vermis after treatment with **ibogaine** or harmaline

30

Neuroscience (Oxford) (1993), 55(2), 303-10

AU

CODEN: NRSCDN; ISSN: 0306-4522

PY

O'Hearn, E.; Molliver, M. E.

AB

1993

The indole alkaloids **ibogaine** and harmaline are .beta.-carboline derivs. that cause both hallucinations and tremor. Reports that **ibogaine** may have potent anti-addictive properties have led to initiatives that it be tested for the treatment of opiate and cocaine addiction. In this study, **ibogaine**-treated rats were analyzed for evidence of neurotoxic effects because human clin. trials of **ibogaine** have been proposed. The authors recently found that **ibogaine** induces a marked glial reaction in the cerebellum with activated astrocytes and microglia aligned in parasagittal stripes within the vermis. Based on those findings, the present study was conducted to investigate whether **ibogaine** may cause neuronal injury or degeneration. The results demonstrate that, after treatment with **ibogaine** or

harmaline, a subset of Purkinje cells in the vermis degenerates. The authors obsd. a loss of the neuronal proteins microtubule-assocd. protein 2 and calbindin co-extensive with loss of Nissl-stained Purkinje cell bodies. Argyrophilic staining of Purkinje cell bodies, dendrites and axons was obtained with the Gallyas reduced silver method for degenerating neurons. Degenerating neurons were confined to narrow parasagittal stripes within the vermis. The authors conclude that both ibogaine and harmaline have selective neurotoxic effects which lead to degeneration of Purkinje cells in the cerebellar vermis. The longitudinal stripes of neuronal damage may be related to the parasagittal organization of the olivocerebellar climbing fiber projection. Since these drugs produce sustained activation of inferior olivary neurons, the authors hypothesize that release of an excitatory amino acid from climbing fiber synaptic terminals may lead to excitotoxic degeneration of Purkinje cells.

ANSWER 12 OF 28 CA COPYRIGHT 1994 ACS

119:262348 CA

Inhibitory effects of ibogaine on cocaine self-administration in rats

Eur. J. Pharmacol. (1993), 241(2-3), 261-5

CODEN: EJPHAZ; ISSN: 0014-2999

Cappendijk, Susanne L. T.; Dzoljic, Michailo R. 1993

In order to det. the potential antiaddictive properties of ibogaine, the cocaine self-administration model was used in rats. A single injection of ibogaine (40 mg/kg i.p.) produced a decrease of cocaine intake, which lasted for >48 h. Since the half-life time of ibogaine is short, this might suggest the involvement of one or several active metabolites of ibogaine in regulating cocaine intake. Repetitive administration of ibogaine on 3 consecutive days also induced a pronounced decrease of cocaine intake. However, a more prominent inhibitory effect on cocaine intake was obsd. in animals treated repeatedly with ibogaine, 40 mg/kg i.p. once each week for 3 consecutive weeks. These results indicate that ibogaine or its metabolite(s) is a long-lasting interruptor of cocaine dependence, which supports similar observations from uncontrolled clin. studies.

ANSWER 13 OF 28 CA COPYRIGHT 1994 ACS

118:167251 CA

Modulation of neopterin release by human Kupffer cells in culture: possible implication in clinical monitoring of HIV-seropositive subjects

Cells Hepatic Sinusoid (1991), 3, 414-16

CODEN: CHSIEL

Keller, F.; Schmitt, C.; Schmitt, M. P.; Jaeck, D.; Kirn, A. 1991

Neopterin (NPT) serum levels are used for the biochem. monitoring of human immunodeficiency virus (HIV) seropos. patients and allograft recipients. The aim of this study was to check whether hepatic

macrophages do indeed release NPT and which factors may modulate this release. The material consisted of surgical wedge liver biopsies taken during upper abdominal surgery. The Kupffer cells (KC) were isolated by collagenase perfusion and centrifugal elutriation. Human KC cultures, stimulated with gamma-IFN (.gamma.-IFN), were found to release large amts. of NPT into the culture supernatant. The stimulation with .gamma.-IFN of the NPT secretion by KC had a dose-dependent character, the maximal effect being obsd. at concns. from 400 to 1,000 IU/mL. KC are in permanent contact with the endotoxin (LPS) contained in the portal blood. The authors have therefore evaluated the influence of LPS on the prodn. of NPT in KC previously treated or not with .gamma.-IFN. Bacterial lipopolysaccharide (LPS) stimulated the release of NPT by KC. Because i.v. drug abusers represent an important group among HIV-seropos. subjects, the effect of different concns. of morphine on the prodn. of NPT was evaluated in KC cultures treated or otherwise with .gamma.-IFN. Interestingly enough, the induction of NPT release by .gamma.-IFN could be partially inhibited by the presence in the medium of morphine, an opium alkaloid frequently used by i.v. drugs addicts. The demonstration that the KC do produce NPT is essential. NPT has become a valuable tool for the detection of early stages of infection in allograft recipients is considered as a predictive marker of AIDS in HIV infection. The observation that the NPT release by KC is modulated by substances such as LPS or opioids might help to clarify certain pathol. mechanisms and provide guidance for intervention.

✓ L9
AN
TI
SO
AU
PY
AB

ANSWER 14 OF 28 CA COPYRIGHT 1994 ACS
117:62808 CA
Molecular analysis of cellular responses to opiate use
Fidia Res. Found. Symp. Ser. (1991), 7(Neurotransm. Regul. Gene Transcr.), 233-49
CODEN: FRFSEL; ISSN: 1040-0451
Eberwine, J. H.; Mackler, S. A.
1991

The self-administration of opiates by human subjects and lab. animals results in drug addiction. Opiate alkaloids such as morphine, as well as opioid peptides such as enkephalin have been shown to cause dramatic cellular and behavioral changes. These include development of tolerance (the requirement for a greater dose of a drug with use to achieve the same effect) and phys. dependence (demonstrated by withdrawal of the drug). These stereotypical behaviors result from long periods (day to weeks) to opiate use. Changes in gene expression in the CNS have been assoc. with opiate stimulation and withdrawal from opiate stimulation. Alterations in neuronal gene expression may therefore be crit. to the development of drug addiction. A better understanding of changes in gene transcription in response to drug use may lead to more effective treatment strategies. Expts. are being performed to identify neuronal genes, the expressions of which (as detd. by changes in the levels of their corresponding mRNA transcripts) are altered in response to either opiate stimulation or opiate

stimulation followed by pptd. withdrawal of stimulation.

- 0 L9 ANSWER 15 OF 28 CA COPYRIGHT 1994 ACS
AN 117:40253 CA
TI Interactions of ibogaine and D-amphetamine: in vivo
microdialysis and motor behavior in rats
SO Brain Res. (1992), 579(1), 87-92
CODEN: BRREAP; ISSN: 0006-8993
AU Maisonneuve, I. M.; Keller, R. W., Jr.; Glick, S. D.
PY 1992
AB Ibogaine, an indolalkylamine, has been proposed for use in treating stimulant addiction. In the present study the authors sought to det. if ibogaine had any effects on the neurochem. and motor changes induced by D-amphetamine that would substantiate the anti-addictive claim. Ibogaine (40 mg/kg, i.p.) injected 19 h prior to a D-amphetamine challenge (1.25 mg/kg, i.p.) potentiated the expected rise in extracellular dopamine levels in the striatum and in the nucleus accumbens, as measured by microdialysis in freely moving rats. Using photocell activity cages, the same ibogaine pretreatment enhanced the stimulatory motor effects induced by a wide range of D-amphetamine doses (0.625, 1.25, 2.5 or 5 mg/kg, i.p.). These findings suggest that ibogaine might increase the reinforcing efficacy of D-amphetamine. However, since high doses of D-amphetamine can be aversive, the potentiation of D-amphetamine's effects by ibogaine might also lead to a decrease in the reinforcing efficacy of D-amphetamine.
- 0 L9 ANSWER 16 OF 28 CA COPYRIGHT 1994 ACS
AN 116:100980 CA
TI A rapid method for interrupting or attenuating poly-drug dependency syndromes
SO PCT Int. Appl., 15 pp.
CODEN: PIXXD2
IN Lotsof, Howard S.
AI WO 91-US3781 910530
PI WO 9118609 A1 911212
PY 1991
AB The administration of ibogaine, ibogamine, tabernanthine, or their nontoxic salts interrupts the physiol. and psychol. aspects of poly-drug dependency to heroin, cocaine, alc., nicotine, caffeine, amphetamine, desoxyephedrine, or methadone in combinations thereof. A single treatment or series of treatments may be effective for 1-18 mo or longer. A patient addicted to alc., cocaine, and heroin was treated with ibogaine; a single dose of ibogaine at 15 mg/kg body wt. completely interrupted heroin and cocaine use and diminished alc. use by 50-80 % on a daily basis.
- 0 L9 ANSWER 17 OF 28 CA COPYRIGHT 1994 ACS
AN 114:240516 CA
TI Effects and aftereffects of ibogaine on morphine self-administration in rats

SO
AU
PY
AB

Eur. J. Pharmacol. (1991), 195(3), 341-5
CODEN: EJPHAZ; ISSN: 0014-2999
Glick, S. D.; Rossman, K.; Steindorf, S.; Maisonneuve, I. M.;
Carlson, J. N.
1991

Ibogaine, a naturally occurring alkaloid, is effective in treating addiction to opiate and stimulant drugs. Ibogaine may reduce the i.v. self-administration of morphine in rats. Ibogaine dose-dependently (2.5-80 mg/kg) decreased morphine intake in the hour after ibogaine treatment (acute effect) and, to a lesser extent, a day later (after-effect). While the acute effect could be attributed to abnormal motor behavior (whole body tremors), the after-effect occurred at a time when ibogaine was eliminated from the body and there was no obvious indication of ibogaine exposure. In some rats, there was a persistent decrease in morphine intake for several days or weeks after a single injection of ibogaine. Other rats began to show such persistent changes only after two or three weekly injections, whereas a few rats were apparently resistant to prolonged after-effects. After-effects could not be attributed to a conditioned aversion. Although ibogaine also depressed the acute responding in rats trained to bar-press for water, there was no evidence of any after-effect a day or more later. The interaction between ibogaine and morphine reinforcement was therefore somewhat specific. Further studies are needed to characterize the nature of the ibogaine-morphine interaction as well as to det. if ibogaine also affects the self-administration of other drugs..

0 L9
AN
TI
SO
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AB

ANSWER 18 OF 28 CA COPYRIGHT 1994 ACS
112:32041 CA
Treatment of alcohol dependence with
ibogaine
U.S., 4 pp.
CODEN: USXXAM
Lotsof, Howard S.
US 88-221030 880718
US 4857523 A 890815
1989

Ibogaine and its salts (4-25 mg/kg orally) are useful for treatment of alc. dependence. A single treatment is effective for .apprx.6 mo. Ibogaine acts as a stimulant with auditory and visual side effects during the first 30 h. Thus, a rat drinking an av. of 32 mL EtOH/day, with access to a choice of EtOH or water, was given ibogaine-HCl (60 mg/kg/day by gavage) for 5 days. Alc. consumption decreased by 53% over the next 30 days.

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ANSWER 19 OF 28 CA COPYRIGHT 1994 ACS
108:544 CA
Incidence of morphine withdrawal and quasi-abstinence syndrome in a model of chronic pain in the rat

SO
AU
PY
AB

Neurosci. Lett. (1987), 81(1-2), 155-8
CODEN: NELED5; ISSN: 0304-3940
Lerida, M.; Sanchez-Biazquez, P.; Garzon, J.
1987

The development of tolerance to and dependence on morphine was studied in a model of exptl. chronic pain in the rat (Freund's adjuvant-induced arthritis). Animals were rendered tolerant by s.c. implantation of 3 75-mg morphine pellets. The pain-suffering rats developed tolerance to the analgesic effect of the alkaloid at a slower rate than control animals. Moreover, upon treatment with naloxone, the rats with arthritis showed a lower incidence of several withdrawal symptoms, particularly jumping, chattering, ptosis, writhing, body shakes, and squeaking on touch. Animals suffering from chronic pain may have an altered physiol. response to the continuous inhibitory effect of exogenous opioids. These differences do not seem to involve cAMP mediated mechanisms since the response to 3-isobutyl-1-methylxanthine was similar in control and arthritic rats.

✓ L9
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ANSWER 20 OF 28 CA COPYRIGHT 1994 ACS
107:169232 CA

A cyclic somatostatin analog that precipitates withdrawal in morphine-dependent mice

SO NIDA Res. Monogr. (1987), 76(Probl. Drug Depend., 1986), 295-301
CODEN: MIDAD4; ISSN: 0361-8595

AU
PY
AB

Shook, J. E.; Pelton, J. T.; Kazmierski, W.; Lemcke, P. K.; Villar, R. G.; Hruby, V. J.; Burks, T. F.
1987

The ability of the mu selective, peptidic, opioid antagonist CTP (D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH₂), to ppt. withdrawal in morphine-dependent mice was evaluated after intracerebroventricular (i.c.v.) and s.c. administration. The withdrawal syndrome evoked by i.c.v. CTP was different in some respects from that obsd. after i.c.v. naloxone. Naloxone, given i.c.v., produced shakes and tremors, defecation, diarrhea, wet dog shakes, jumping and wt. loss. In contrast, the prominent signs following i.c.v. CTP were grooming, tremors and shakes, defecation, wet dog shakes and wt. loss. CTP treated mice exhibited a greatly reduced incidence of jumping behaviors and diarrhea. While s.c. naloxone evoked similar effects to i.c.v. naloxone, CTP given s.c. stimulated defecation and modest wt. loss only. The differences in the profile of withdrawal signs between naloxone and CTP may be related to their differences in receptor selectivity or possibly to their resp. alkaloidal and peptidic natures. The relative lack of behavioral effects seen after s.c. CTP probably reflects the inability of CTP to pass through the blood-brain barrier, and indicates that although the majority of withdrawal signs are mediated by centrally located opioid receptors, the gastrointestinal tract can be withdrawn independently of the central nervous system.

0 L9
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ANSWER 21 OF 28 CA COPYRIGHT 1994 ACS
106:12967 CA

Rapid method for interrupting the cocaine and amphetamine abuse

syndrome
U.S., 4 pp.
CODEN: USXXAM
Lotsof, Howard S.
AI US 85-754836 850715
PI US 4587243 A 860506
PY 1986
AB Cocaine or amphetamine abuse is treated by administration of ibogaine or its salts. For example, a subject previously using 2-4 g d-deoxyephedrine-HCl/wk, when given a single 500-mg capsule of ibogaine, remained stimulant free for 6 mo.

✓ L9 ANSWER 22 OF 28 CA COPYRIGHT 1994 ACS
AN 104:81636 CA
TI Survival responses to new cytostatic hexitols of P388 mouse and K562 leukemia cells in vitro
SO Cancer Treat. Rep. (1986), 70(2), 279-84
AU CODEN: CTRRDO; ISSN: 0361-5960
PY Palyi, Istvan
AB 1986

The effect of 4 hexitols mitolactol [10318-26-0], dianhydrogalactitol [23261-20-3], 3,4-diacetyldianhydrogalactitol (DiacDAG) [57230-48-5] and 3,4-disuccinyldianhydrogalactitol [66913-57-3], 2 vinca alkaloids (vincristine [57-22-7] and N-formylleurosine [54022-49-0]), doxorubicin [23214-92-8], and methotrexate [59-05-2] on colony formation of P388 and K562 cells were studied and compared. DisuDAG is a new deriv. of hexitols with favorable therapeutic indexes on rodent tumors. On the basis of IC50 values in molar concns., dianhydrogalactitol was 5 to 6 times more toxic than DiacDAG, and mitolactol was 36 (K562) or 80 (P388) times more toxic than DisuDAG. N-Formylleurosine was found to be 20 (P388) or 1000 (K562) times less toxic than vincristine. The large difference was due to the high resistance of K562 cells to N-formylleurosine. Both cell lines were very sensitive to doxorubicin: IC50 after 1 h of exposure of P388 cells = 240 nM and after 1 h of exposure of K562 cells = 275 nM. Continuous exposure to methotrexate resulted in 11 and 14.5 nM for P388 and K562 cells, resp. There was no direct correlation between the length of doubling times and drug sensitivity (doubling time of P388 = 13-14 h and of K562 = 25 h). The sensitivity of cell lines was rather tumor-specific and drug-dependent.

0 L9 ANSWER 23 OF 28 CA COPYRIGHT 1994 ACS
AN 102:160426 CA
TI Rapid method for interrupting the narcotic addiction syndrome
SO U.S., 4 pp.
CODEN: USXXAM
IN Lotsof, Howard S.
AI US 83-553138 831118
PI US 4499096 A 850212
PY 1985
AB Ibogaine (I) [83-74-9] interrupts the physiol.

and psychol. aspects of the narcotic addiction syndrome. A single oral treatment with I (6 to 19 mg/kg) disrupted heroin [561-27-3] use in humans for .apprx.6 mo.

✓L9
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ANSWER 24 OF 28 CA COPYRIGHT 1994 ACS
98:193218 CA

Immunological methods for removing species from the blood circulatory system and devices therefor
U.S., 11 pp. Cont. of U.S. Ser. No. 255,154, abandoned.
CODEN: USXXAM

Strahilevitz, Meir
US 77-761290 770121
US 4375414 A 830301
1983

Hapten-removing devices used with immunol. methods for the removal of psychotropics such as psychoactive N,N-dimethyltryptamines, phenanthrene alkaloids, psychomimetic indoles and psychoactive amphetamines from the blood of a living mammal are disclosed. The methodol. is based on treating the psychoactive substances as haptens and utilizing their protein conjugates to produce antibodies. Thus, the use of a hapten-removing device with an immunol. method for the treatment of intoxication by psychotropics or for the removal of endogenously-occurring psychoactive haptens in schizophrenia are described.

✓L9
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ANSWER 25 OF 28 CA COPYRIGHT 1994 ACS
97:104155 CA

Analgesic effects of intraventricular morphine and enkephalins in nondependent and morphine-dependent rats
J. Pharmacol. Exp. Ther. (1982), 222(1), 190-7
CODEN: JPETAB; ISSN: 0022-3565

Brady, Linda S.; Holtzman, Stephen G.
1982

The analgesic effects of intracerebroventricular (i.c.v.) morphine (I) [57-27-2] and the enzyme-resistant enkephalin analogs, D-Ala2-Leu- [65189-64-2] and D-Ala2-Met-enkephalinamide [61090-95-7], measured in the tail-flick test, were compared in nondependent and morphine-dependent rats. Dependence was induced and maintained by scheduled access to 0.05% morphine soln. for at least 8 wk before testing. In the nondependent rats, 1.0 to 10 .mu.g of each drug injected into the lateral ventricle produced a dose-related increase in analgesia; on a molar basis, morphine was 1.3 (1.0-1.7) times more potent than the enkephalins. naloxone [465-65-6] (0.3 And 1.0 mg/kg) antagonized the analgesic effect of the 3 compds.: the effect of morphine was competitively antagonized, whereas the interaction between naloxone and the enkephalins did not appear to be competitive. Chronic morphine treatment produced different changes in the analgesic effects of morphine and the enkephalins. In contrast to the tolerance that was obsd. after s.c. injection of morphine in morphine-dependent rats, the analgesic effect of i.c.v. morphine was enhanced in these animals. The analgesic effect of D-Ala2-Leu-enkephalinamide was also enhanced in

morphine-dependent animals, whereas tolerance developed to the effect of D-Ala2-Met-enkephalinamide. Thus, the analgesic effects of morphine and enkephalins are differentially altered in the presence of naloxone and in morphine-dependent animals. These results could reflect an allosteric interaction between neuronal binding sites for enkephalins and opiate alkaloids.

✓ L9
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ANSWER 26 OF 28 CA COPYRIGHT 1994 ACS

97:92608 CA

7,8 And 7-8 substituted 4,5(.alpha.)-epoxymorphinan-6-one compounds, and methods of treating pain and drug dependence with them

U.S., 21 pp. Cont.--in-part of U.S. Ser. No. 911,939, abandoned.
CODEN: USXXAM

Kotick, Michael P.; Schut, Robert N.; Polazzi, Joseph O.; Leland, David L.

US 79-56549 790711

US 4272541 A 810609

1981

The title compds. I (R1 = H, Me; R2 = cyclopropylmethyl, cyclobutylmethyl, allyl, tetrahydrofurfuryl, R3 = .beta.-Me, .beta.-Et, .alpha.-Et, R1 = H, .alpha.-Me) were prepd. Thus, codeinone was treated with EtLi to give 4,5.alpha.-epoxy-8.beta.-ethyl-3-methoxy-17-methylmorphinan-6-one, which was treated with BrCN followed by hydrolysis and treatment with cyclopropylmethyl bromide to give 17-cyclopropylmethyl-4,5.alpha.-epoxy-8.beta.-ethyl-3-methoxymorphinan-6-one-HCl (II). The analgesic ED50 (mouse writhing test) of II was 2.1 mg/kg, and its narcotic antagonist AD50 was 0.78 mg/kg.

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ANSWER 27 OF 28 CA COPYRIGHT 1994 ACS

78:75868 CA

Methadone or propoxyphene tablets for fighting drug addiction
Ger. Offen., 19 pp.

CODEN: GWXXBX

Franklin, Irving; Berk, Jerome

DE 2217132 721026

1972

Since aq. solns. of methadone-HCl may be misused, concd. solns. too viscous to inject and soly. changes in the drug were developed. Tablets for fighting drug abuse contained the H2O-sol. HCl and a pptg. agent, which may be a pharmaceutically tolerated alkalizing agent which when dissolved in H2O produces an alk. pH, or an alkaloid precipitant which acts in nonacid conditions, or a combination of both, together with the usual tableting components. The therapeutic agents may be methadone, propoxyphene or their acid salts and the alk. agents NaHCO3 or Na2HPO4. Tannic acid may be employed as the precipitant. The tablet may also contain a component which increases the viscosity of the soln. in ratios of 10:1 to 40:1 additive to drug. Thus, tablets contg. methadone-HCl 0.5, lactose 6.0, mannitol 2.0, starch 2.5, Na2HPO4 0.25, Na CM-cellulose 0.5, Me cellulose 0.5, Na

saccharin 0.2, and Zn stearate 0.75 parts were prepd.

✓L9

ANSWER 28 OF 28 CA COPYRIGHT 1994 ACS
71:47510 CA

TI Psychopharmacology and opiate dependence

SO U.S., Public Health Serv. Publ. (1967), Volume Date 1957-1967, No.
1836, 853-64

CODEN: XPHPAW

AU Jaffe, Jerome H.

PY 1967

AB A review. The psychopharmacology of opiates and opiates dependence,
drugs used in the control of withdrawal symptoms, and the
pharmacotherapy and treatment of narcotic
dependence are discussed. 48 references.

FILE 'BIOSIS' ENTERED AT 10:53:41 ON 30 SEP 94
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FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNS) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 23 September 1994 (940923/ED)

CAS REGISTRY NUMBERS (R) LAST ADDED: 24 September 1994 (940924/UP)

As of December 31, 1993 the BIOSIS File will be updated weekly with
information from both publications. SDIs will now be run weekly. For
more information enter HELP UPDATE and HELP COST at an arrow
prompt(=>).

68 L1

0 NORIBOGAIN?

75 IBOGAIN?

23075 ALKALOID?

49 TABERNANTH?

272172 T

88 IBOGA

26 (TABERNANTH? OR T) (W) IBOGA

357166 12

0 METHOXYIBOGAMIN?

17562 METHOXY

37 IBOGAMIN?

0 METHOXY IBOGAMIN?

(METHOXY(W) IBOGAMIN?)

0 12(W) (METHOXYIBOGAMIN? OR METHOXY IBOGAMIN?)

L11 23133 L1 OR (NORIBOGAIN? OR IBOGAIN? OR ALKALOID? OR (TABERNANTH
? OR T) (W) IBOGA OR 12(W) (METHOXYIBOGAMIN? OR METHOXY IBOGA
MIN?))

=> s l11 and ((substance? or drug# or alcohol? or narcotic? or drink? or
chemical?)(3a)(depend? or withdraw? or crave? or abuse?))

```

98474 SUBSTANC?
1225448 DRUG#
88719 ALCOHOL?
6341 NARCOTIC?
28650 DRINK?
193467 CHEMICAL?
482855 DEPEND?
25512 WITHDRAW?
684 CRAV?
22069 ABUS?
30407 (SUBSTANC? OR DRUG# OR ALCOHOL? OR NARCOTIC? OR DRINK? OR
CHEMICAL?) (3A) (DEPEND? OR WITHDRAW? OR CRAV? OR ABUS?)
L12 113 L11 AND ((SUBSTANC? OR DRUG# OR ALCOHOL? OR NARCOTIC? OR D
RINK? OR CHEMICAL?) (3A) (DEPEND? OR WITHDRAW? OR CRAV? OR A
BUS?))
=> s l12 and (treat? or therap?)
877307 TREAT?
404501 THERAP?
L13 32 L12 AND (TREAT? OR THERAP?)
=> fil medl; s l13
FILE 'MEDLINE' ENTERED AT 11:00:05 ON 30 SEP 94
FILE LAST UPDATED: 20 SEP 1994 (940920/UP). FILE COVERS 1966 TO DATE.
+QLF/CT SHOWS YOU THE ALLOWABLE QUALIFIERS OF A TERM.
>>>> MESH SUBHEADING PRE-EXPLOSIONS CAN BE USED--SEE HELP PRE <<<<
** If you post-qualify L-numbered answer sets with limiters **
** (e.g., L4/MAJ), you MUST have highlighting set ON when **
** creating the initial L-numbered answer set to ensure full **
** recall. Type D SET HIGH at an arrow prompt to verify **
** your current setting for highlighting. **
37 L1
0 NORIBOGAIN?
45 IBOGAIN?
15895 ALKALOID?
17 TABERNANTH?
1780669 T
22 IBOGA
4 (TABERNANTH? OR T) (W) IBOGA
269038 12
0 METHOXYIBOGAMIN?
6529 "METHOXY"
6 IBOGAMIN?
0 METHOXY IBOGAMIN?
("METHOXY"(W) IBOGAMIN?)
0 12 (W) (METHOXYIBOGAMIN? OR METHOXY IBOGAMIN?)
127422 SUBSTANC?
1694025 DRUG#

```

```

123892 ALCOHOL?
14939 NARCOTIC?
39884 DRINK?
433864 CHEMICAL?
425427 DEPEND?
30082 WITHDRAW?
658 CRAV?
41981 ABUS?
56274 (SUBSTANC? OR DRUG# OR ALCOHOL? OR NARCOTIC? OR DRINK? OR
CHEMICAL?) (3A) (DEPEND? OR WITHDRAW? OR CRAV? OR ABUS?)
953503 TREAT?
1355924 THERAP?
L14 71 L12 AND (TREAT? OR THERAP?)

=> s l14 and (pharmac? or comp?)
1249820 PHARMAC?
2906648 COMP?
L15 49 L14 AND (PHARMAC? OR COMP?)

=> s ((ibogaine or d3.132.) and (substance abuse or substance dependence
or alcoholism+nt))/ct
41 IBOGAIN/CT
192212 D3.132./CT
18286 SUBSTANCE ABUSE/CT
14621 SUBSTANCE DEPENDENCE/CT
42599 ALCOHOLISM+NT/CT (12 TERMS)
L16 6871 ((IBOGAIN OR D3.132.) AND (SUBSTANCE ABUSE OR SUBSTANCE D
EPENDENCE OR ALCOHOLISM+NT))/CT

=> s l16 and (drug therapy or therapy or therapeutic use)/ct
597562 DRUG THERAPY/CT
461567 THERAPY/CT
646771 THERAPEUTIC USE/CT
L17 1882 L16 AND (DRUG THERAPY OR THERAPY OR THERAPEUTIC USE)/CT

=> s ((ibogaine or d3.132.) (l) (drug therapy or therapy or therapeutic
use))/ct
41 IBOGAIN/CT
192212 D3.132./CT ← Alkaloids
597562 DRUG THERAPY/CT
461567 THERAPY/CT
646771 THERAPEUTIC USE/CT
L18 31773 ((IBOGAIN OR D3.132.) (L) (DRUG THERAPY OR THERAPY OR THERA
PEUTIC USE))/CT

=> s (ibogaine(l) (drug therapy or therapy or therapeutic use))/ct
41 IBOGAIN/CT
597562 DRUG THERAPY/CT
461567 THERAPY/CT
646771 THERAPEUTIC USE/CT
L19 2 (IBOGAIN(L) (DRUG THERAPY OR THERAPY OR THERAPEUTIC USE))/
CT

```

=> s (ibogaine and (substance abuse or substance dependence or alcoholism+nt))/ct
 41 IBOGAINE/CT
 18286 SUBSTANCE ABUSE/CT
 14621 SUBSTANCE DEPENDENCE/CT
 42599 ALCOHOLISM+NT/CT (12 TERMS)
 L20 2 (IBOGAINE AND (SUBSTANCE ABUSE OR SUBSTANCE DEPENDENCE OR ALCOHOLISM+NT))/CT
 => s 15 or 119 or 120; fil embas; s 113
 238085 15
 L21 238087 15 OR L19 OR L20

FILE 'EMBASE' ENTERED AT 11:42:42 ON 30 SEP 94
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FILE COVERS 1974 TO 21 Sep 1994 (940921/ED)

=> s 115 or 119 or 120; fil embas; s 113
 L22 50 L15 OR L19 OR L20

FILE 'EMBASE' ENTERED AT 11:43:53 ON 30 SEP 94
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FILE COVERS 1974 TO 21 Sep 1994 (940921/ED)

35 L1
 0 NORIBOGAIN?
 81 IBOGAIN?
 12005 ALKALOID?
 30 TABERNANTH?
 196611 T
 14 IBOGA
 5 (TABERNANTH? OR T) (W) IBOGA
 252598 12
 1 METHOXYIBOGAMIN?
 10454 "METHOXY"
 17 IBOGAMIN?
 0 METHOXY IBOGAMIN?
 ("METHOXY"(W) IBOGAMIN?)
 1 12 (W) (METHOXYIBOGAMIN? OR METHOXY IBOGAMIN?)
 79389 SUBSTANC?
 1679440 DRUG#
 83809 ALCOHOL?
 8663 NARCOTIC?
 29084 DRINK?
 681386 CHEMICAL?
 397253 DEPEND?
 31718 WITHDRAW?
 712 CRAV?

34726 ABUS?
 52843 (SUBSTANC? OR DRUG# OR ALCOHOL? OR NARCOTIC? OR DRINK? OR
 CHEMICAL?)(3A)(DEPEND? OR WITHDRAW? OR CRAV? OR ABUS?)
 917924 TREAT?
 1583253 THERAP?
 L23 142 L12 AND (TREAT? OR THERAP?)

 => s 123 and (composition# or compound# or comp## or pharmac?)
 63227 COMPOSITION#
 441610 COMPOUND#
 2298 COMP##
 774618 PHARMAC?
 L24 88 L23 AND (COMPOSITION# OR COMPOUND# OR COMP## OR PHARMAC?)

 => dup rem 113,122,124
 FILE 'BIOSIS' ENTERED AT 11:50:35 ON 30 SEP 94
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 FILE 'EMBASE' ENTERED AT 11:50:35 ON 30 SEP 94
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 PROCESSING COMPLETED FOR L13
 PROCESSING COMPLETED FOR L22
 PROCESSING COMPLETED FOR L24
 L25 134 DUP REM L13 L22 L24 (36 DUPLICATES REMOVED)

 => s 124 and (human# or mammal?)
 2490092 HUMAN#
 1092802 MAMMAL?
 L26 55 L24 AND (HUMAN# OR MAMMAL?)

 => dup rem 113,122,126
 FILE 'BIOSIS' ENTERED AT 11:53:23 ON 30 SEP 94
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 FILE 'MEDLINE' ENTERED AT 11:53:23 ON 30 SEP 94

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 PROCESSING COMPLETED FOR L13
 PROCESSING COMPLETED FOR L22
 PROCESSING COMPLETED FOR L26
 L27 104 DUP REM L13 L22 L26 (33 DUPLICATES REMOVED)

 => d 1-104 an ti au so ab; fil ca; s (12(w)hydroxy(w)(ibogamin? or
 hydroxyibogamin?))/ab,bi

 0 L27 ANSWER 1 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 1
 AN 94:319813 BIOSIS
 TI The putative anti-addictive drug ibogaine is a competitive
 inhibitor of (3H)MK-801 binding to the NMDA receptor complex.
 AU Popik P; Layer R T; Skolnick P

- SO Psychopharmacology 114 (4). 1994. 672-674. ISSN: 0033-3158
 AB Ibogaine is a putative anti-addictive drug with potential efficacy for the treatment of opiate, stimulant, and alcohol abuse. We now report ibogaine is a competitive inhibitor (K-i, 1.01 +/- 0.1 mu-M) of (3H)MK-801 binding to N-methyl-D-aspartate (NMDA) receptor coupled cation channels. Since MK-801 can attenuate the development of tolerance to morphine and alcohol as well as sensitization to stimulants in preclinical studies, the reported ability of ibogaine to modify drug-seeking behavior in man may be attributable to a blockade of NMDA receptor coupled cation channels.
- ✓L27 ANSWER 2 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
 AN 94185401 EMBASE
 TI Pharmacodynamics and pharmacokinetics of khat: A controlled study.
 AU Widler P.; Mathys K.; Brenneisen R.; Kalix P.; Fisch H.-U.
 SO CLIN. PHARMACOL. THER., (1994) 55/5 (556-562).
 ISSN: 0009-9236 CODEN: CLPTAT
- AB Objectives: To show the subjective and cardiovascular effects of khat leaves having a standardized content of cathinone. Background: The main effect of khat is an increase of energy and alertness. This effect is thought to be attributable to the phenylalkylamine cathinone, but no controlled clinical trials have been published. Design: The design was balanced and double blind. Six drug-naive volunteers received a single dose of khat corresponding to 0.8 mg/kg body weight, as well as alkaloid-free khat as a placebo. Psychologic effects were evaluated by the Addiction Research Center Inventory (ARCI) and visual analog scales. Physiologic measures were systolic blood pressure, diastolic blood pressure, and heart rate. Plasma concentrations of cathinone and its metabolites norephedrine and R,R-(+)-norpseudoephedrine were determined by HPLC. Results: Maximal plasma concentrations of cathinone (127 +/- 53 [SD] ng/ml) were attained after 127 +/- 30 minutes. The area under the plasma concentration-time curve from 0 to 9 hours was 415 +/- 207 ng/ml .cntdot. hr, and the terminal elimination half-life was 260 +/- 102 minutes. An effect of khat was observed in the ARCI scales Abuse Potential (p < 0.01), Motor Stimulation (p < 0.02), Amphetamine-Like Effect (p < 0.005), and Stimulation-Euphoria (p < 0.005), as well as in the visual analog scales Excited-Calm (p < 0.001) and Energetic-Lethargic (p < 0.001). Conclusions: Our results provide objective evidence for the amphetamine-like stimulatory effects of khat leaves. These effects were closely similar to those observed after cathinone, 0.5 mg/kg body weight, although peak plasma concentrations of cathinone after khat were delayed.
- ✓L27 ANSWER 3 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
 AN 94267046 EMBASE
 TI A preliminary investigation of ibogaine: Case reports and recommendations for further study.
 AU Sheppard S.G.
 SO J. SUBST. ABUSE TREAT., (1994) 11/4 (379-385).
 ISSN: 0740-5472 CODEN: JSATEG

AB

A naturally occurring substance, ibogaine, was taken by seven individuals who were addicted to opiates. Ibogaine, an alkaloid with psychotropic effects at doses of 200-300 mg and above, was taken in single doses of 700-1800 mg by the subjects in the study. At the end of the 24-38-hr psychoactive period induced by the drug at these doses, none of the subjects displayed significant opiate withdrawal symptoms. At the lowest dose of 700 mg, one subject discontinued his drug abuse after 2 days; of the remaining six individuals who took 1,000 mg or above, two relapsed after a number of weeks, one reverted to intermittent heroin use, and three appear to have remained drug-free 14 weeks or more after undergoing this experimental treatment. Ibogaine may be of value in the present and could serve as a model for the development of improved agents for the treatment of substance abuse in the future.

L27

ANSWER 4 OF 104 MEDLINE
94282580 MEDLINE

DUPLICATE 2

TI

Antagonists at excitatory opioid receptors on sensory neurons in culture increase potency and specificity of opiate analgesics and attenuate development of tolerance/dependence.

AU

Shen KF; Crain SM

SO

Brain Res, (1994 Feb 14) 636 (2) 286-97.

AB

Journal code: B5L. ISSN: 0006-8993.
At low (< nM) concentrations, mu, delta or kappa opioid peptides as well as morphine and other opioid alkaloids elicit dose-dependent excitatory prolongation of the calcium-dependent component of the action potential duration (APD) of many mouse sensory dorsal root ganglion (DRG) neurons, whereas application of the same opioids at higher (uM) concentrations results in inhibitory shortening of the APD. These bimodal opioid excitatory/inhibitory effects on DRG neurons are blocked by naloxone. In contrast to bimodally acting opioids, the opioid alkaloids, etorphine and dihydroetorphine (thebaine-oripavine derivatives) uniquely elicited only dose-dependent, naloxone-reversible inhibitory effects on sensory neurons in DRG-spinal cord explants, even at concentrations as low as 1 pM, and showed no excitatory effects at lower concentrations. These remarkably potent inhibitory opioid receptor agonists also act as antagonists at excitatory opioid receptors since pretreatment of DRG neurons with subthreshold concentrations (< pM) blocked excitatory APD prolongation by nM morphine (or other opioids) and unmasked inhibitory APD shortening which generally requires much higher concentrations. Furthermore, acute application of pM-nM etorphine to chronic microM morphine- or D-Ala2-D-Leu5 enkephalin (DADLE)-treated DRG neurons blocked the nM naloxone-precipitated APD prolongation that generally occurs in DRG cells sensitized by bimodally acting opioids. In the presence of pM etorphine, chronic treatment of DRG neurons with microM morphine or DADLE no longer resulted in development of tolerance/dependence effects, as previously observed after similar chronic opioid treatment in the presence of cholera

toxin-B subunit. These in vitro studies may clarify the mechanisms underlying the potent analgesic effects of etorphine and dihydroetorphine in vivo and to guide the use of these and other excitatory opioid receptor antagonists in attenuating development of opiate dependence/addiction.

✓L27

AN 94138754 EMBASE ANSWER 5 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

TI Use and abuse of analgesics in tension-type headache.

AU Schnider P.; Aull S.; Mraz M.; Travniczek A.; Zeiler K.; Wessely P.
SO CEPHALALGIA, (1994) 14/2 (162-167).

ISSN: 0333-1024 CODEN: CEPHDF

AB Eighty patients suffering from tension-type headache for an average of 21 years were asked to report on all drugs they had ever taken (type, dosage, duration of intake, efficacy) or were taking currently. The patients had consumed on average 6.3 different drugs. The cumulative doses of derivatives of para-aminophenol, pyrazolone, and salicylic acid in some cases reached a maximum of several kilograms. Most drugs were classified by the patients as 'moderately effective'. The rating 'very effective' was assigned primarily to barbiturates; however, barbiturates are no longer used as components of compound analgesic drugs in Austria. At the time of investigation, patients consumed 2.5 (mean) different drugs, primarily as compound preparations. Seventeen patients (21%) showed signs of possible analgesics- or ergotamine-induced headache and were therefore advised to undergo withdrawal therapy. Our results show that patients with tension-type headache are at considerable risk of becoming drug-dependent and of acquiring analgesics-induced headache.

0 L27

AN 94159648 MEDLINE ANSWER 6 OF 104 MEDLINE

TI Ibogaine reduces preference for cocaine consumption in

AU Sershen H; Hashim A; Lajtha A
SO Pharmacol Biochem Behav, (1994 Jan) 47 (1) 13-9.

Journal code: P3Q. ISSN: 0091-3057.

AB After a period of forced exposure to 300 mg/1 cocaine HCl in drinking water for a period of one week, followed by forced exposure to 200 mg/1 cocaine for an additional week, male C57BL/6By mice developed a preference for cocaine when given a choice of drinking either water or a solution containing cocaine (200 mg/1). The mean daily intake of cocaine during the choice period was 26 +/- 1 mg/kg or, when expressed as the ratio of cocaine over total fluid intake, represented a cocaine preference of 71 +/- 2%. Administration of ibogaine HCl (40 mg/kg, two injections 6 h apart) two weeks after the beginning of the choice period reduced the cocaine preference for at least five days; the mean daily intake of cocaine was reduced by 38% (to 16 +/- 1 mg/kg per day; p < 0.05) and cocaine preference was reduced to 41 +/- 2% (cocaine fluid consumption/total fluid intake). An acute challenge injection of cocaine (25 mg/kg SC) produced a significant increase in cocaine-induced locomotor activity and stereotypy in mice previously exposed to cocaine in

their drinking water (cocaine choice group). Five days after ibogaine administration, locomotor and stereotypy activity were significantly lower after a challenge injection of cocaine (25 mg/kg SC). Brain levels of cocaine 35 min after the challenge injection of cocaine were approximately 25% higher in ibogaine-treated mice (7.2 +/- 0.5 and 9.3 +/- 0.8 micrograms/g wet wt for water vs. mice treated with water plus ibogaine and 9.3 +/- 0.2 and 11.8 +/- 0.7 micrograms/g wet wt for cocaine drinking vs. cocaine drinking plus ibogaine treatment). (ABSTRACT TRUNCATED AT 250 WORDS)

✓ L27 ANSWER 7 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS
 AN 94:51404 BIOSIS
 TI A gas chromatography-mass spectrometry (GCMS) method for ibogaine.
 AU Keefner S M; Hough L B; Gallagher C A; Seyed-Mozaffari A; Archer S; Glick S D
 SO 23rd Annual Meeting of the Society for Neuroscience, Washington, D.C., USA, November 7-12, 1993. Society for Neuroscience Abstracts 19 (1-3). 1993. 1024. ISSN: 0190-5295

✓ L27 ANSWER 8 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
 AN 93101468 EMBASE
 TI Ibogaine induces glial activation in parasagittal zones of the cerebellum.
 AU O'Hearn E.; Long D.B.; Molliver M.E.
 SO NEUROREPORT, (1993) 4/3 (299-302).
 ISSN: 0959-4965 CODEN: NERPEZ
 AB Ibogaine, an indole alkaloid, has been proposed for treatment of drug addiction, yet its mechanism, site of action, and possible neurotoxicity have not been determined. Since neuronal injury is known to activate neuroglial cells, we investigated potential neurotoxic effects of this drug in rats by examining expression of specific glial markers. After treatment with ibogaine (100 mg kg⁻¹ i.p.; 1-3 doses), we observed increased cytochemical markers in both microglia (OX-6, OX-42, W3/25) and astrocytes (GFAP), associated with striking morphologic changes in these cells. Activated glial cells were restricted to longitudinally oriented, parasagittal stripes within the vermis of cerebellar cortex. The ibogaine-induced activation of cerebellar glial cells is highly suggestive of neuronal degeneration, most likely of Purkinje cells.

✓ L27 ANSWER 9 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 3
 AN 94:213804 BIOSIS
 TI Efficacy of camptothecin congeners in the treatment of human breast carcinoma xenografts.
 AU Pantazis P; Kozielecki A J; Vardeman D M; Petry E R; Giovanella B C
 SO Oncology Research 5 (8). 1993 (1994). 273-281.
 AB We have shown recently that the plant alkaloid camptothecin and some of its derivatives inhibit growth of human breast carcinoma cells in vitro and induce complete regression of human breast tumors

grown in nude mice. Because of the use of camptothecin derivatives in several clinical studies with patients bearing various types of cancer, in this report, we have investigated and described parameters and conditions that can modulate the anticancer effectiveness and cytotoxicity of these drugs when administered as suspensions. It is demonstrated that the antitumor effectiveness and drug-induced toxicity depend on the camptothecin derivative, the drug dose administered, the route of administration, and the scheduling of drug administration. 9-aminocamptothecin administered i.m. generates the best results, but for all practical purposes, 9-nitrocamptothecin administered orally appeared to be the camptothecin derivative and route of administration of choice. Further, we report the partial response of one breast tumor to camptothecin and propose that this tumor may require chemotherapy with a camptothecin derivative followed by an anticancer drug with a different mechanism of cell-killing activity.

D L27 ANSWER 10 OF 104 MEDLINE
 AN 94062953 MEDLINE
 TI Inhibitory effects of ibogaine on cocaine self-administration in rats.
 AU Cappendijk SL; Dzoljic MR
 SO Eur J Pharmacol, (1993 Sep 14) 241 (2-3) 261-5.
 AB

DUPLICATE 4

In order to determine the potential anti-addictive properties of ibogaine, we used the cocaine self-administration model in rats. The results indicate that a single injection of ibogaine (40 mg/kg i.p.) produced a significant decrease of cocaine intake, which remained unaltered for more than 48 h. Since the half-life time of ibogaine is short, this might suggest the involvement of one or several active metabolites of ibogaine in cocaine intake. Repetitive administration of ibogaine on three consecutive days also induced a pronounced decrease of cocaine intake. However, a more prominent inhibitory effect on cocaine intake was observed in animals treated repeatedly with ibogaine (40 mg/kg i.p.), once each week for 3 consecutive weeks. These results indicate that ibogaine or its metabolite(s) is a long-lasting interruptor of cocaine dependence, which supports similar observations from uncontrolled clinical studies.

✓ L27 ANSWER 11 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS
 AN 94:162330 BIOSIS
 TI Multidrug resistance (MDR) genes in haematological malignancies.
 AU Nooter K; Sonneveld P
 SO Cytotechnology 12 (1-3). 1993. 213-230. ISSN: 0920-9069
 AB

The emergence of drug resistant cells is one of the main obstacles for successful chemotherapeutic treatment of haematological malignancies. Most patients initially respond to chemotherapy at the time of first clinical admission, but often relapse and become refractory to further treatment not only to the drugs used in the first treatment but also to a variety of other drugs. Laboratory investigations have now provided a cellular basis for this clinical observation of multidrug resistance (MDR).

Expression of a glycoprotein (referred to as P-glycoprotein) in the membrane of cells made resistant in vitro to naturally occurring anticancer agents like anthracyclines, Vinca alkaloids and epipodophyllotoxins, has been shown to be responsible for the so-called classical MDR phenotype. P-glycoprotein functions as an ATP-dependent, unidirectional drug efflux pump with a broad substrate specificity, that effectively maintains the intracellular cytotoxic drug concentrations under a non-cytotoxic threshold value. Extensive clinical studies have shown that P-glycoprotein is expressed on virtually all types of haematological malignancies, including acute and chronic leukaemias, multiple myelomas and malignant lymphomas. Since in model systems for P-glycoprotein-mediated MDR, drug resistance may be circumvented by the addition of non-cytotoxic agents that can inhibit the outward drug pump, clinical trials have been initiated to determine if such an approach will be feasible in a clinical situation. Preliminary results suggest that some haematological malignancies, among which are acute myelocytic leukaemia, multiple myeloma and non-Hodgkin's lymphoma, might benefit from the simultaneous administration of cytotoxic drugs and P-glycoprotein inhibitors. However, randomised clinical trials are needed to evaluate the use of such resistance modifiers in the clinic.

✓L27

AN 93:507198 BIOSIS
 TI EFFECT OF COCAINE AND MORPHINE ON NEUTRAL ENDOPEPTIDASE ACTIVITY OF HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS CULTURED WITH LECTINS.
 AU LEONI L M; LOSA G A
 SO CELL BIOCHEM FUNCT 11 (3). 1993. 211-219. CODEN: CBFUDH ISSN: 0263-6484

AB

We have tested the effect of alkaloids (cocaine, morphine) and enkephalins on neutral endopeptidase of peripheral blood mononuclear cells activated by lectins. When treated with concanavalin A and cocaine, peripheral blood mononuclear cells showed an enhanced activity (+110 per cent) of the membrane neutral endopeptidase, which was not related to the expression of the common acute lymphoblastic leukemia antigen at the cell surface, although both molecules have the identical amino acid sequence. Phytohemagglutinin-P, morphine and synthetic enkephalins did not induce the activity of neutral endopeptidase nor the expression of common acute lymphoblastic leukemia antigen. Our findings suggested that the drugs of abuse, cocaine and morphine, affected specific membrane constituents without altering proliferation, subcellular localization of membrane enzymes or the surface immune phenotype of peripheral blood mononuclear cells.

✓L27

AN 94:7846 BIOSIS
 TI Preformulation and development of ibogaine injection for the treatment of drug abuse.

AU Matharu R P; Parikh B; Murty R

SO AAPS (American Association of Pharmaceutical Scientists) Eighth Annual Meeting and Exposition, Orlando, Florida, USA, November 14-18,

0 L27
AN 94:39545 BIOSIS
TI Comparison of the behavioral effects of ibogaine from three
AU Schechter M D; Gordon T L
SO European Journal of Pharmacology 249 (1). 1993. 79-84. ISSN:
0014-2999

AB Ibogaine is an alkaloid employed for its hallucination. properties in West Central Africa which has been the subject of alleged efficacy as an aid in the interruption and treatment of chemical dependency. The major sources of the Schedule I agent are: Sigma Chemical Co., the National Institute on Drug Abuse and as NDA International Inc.'s Endabuse. The intent of the present study was to, for the first time, train rats to discriminate the interoceptive stimuli produced by (10 mg/kg, intraperitoneally administered) ibogaine. Once trained, these rats were used to investigate the dose-response effects to ibogaine from each of the three suppliers. In addition, stimulus generalization to the dopamine antagonist CGS 10476B, as well as to the serotonergically active compounds fenfluramine, TFMPP (1-(m-trifluoromethylphenyl)piperazine), DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane), MDMA (3,4-methylenedioxymethamphetamine), quipazine and LSD, was tested. The results indicate that ibogaine is readily discriminable from its vehicle and that ibogaine from each of the three supplies produced statistically similar discrimination with ED-50 values ranging from 2.5 to 3.4 mg/kg. In addition, various doses of the novel drugs tested produced, at best, intermediate ibogaine-appropriate responding and, thus, no drug tested can be considered to generalize to ibogaine-like stimuli. Discussion concerns the multiple actions of ibogaine that have been cited in the scientific literature. The similarity in potency of ibogaine from three potential suppliers should allow for pre-clinical work using any of these research samples to be comparable.

✓ L27
AN 92358911 EMBASE
TI Inhibition of respiratory burst activity in alveolar macrophages by bisbenzylisoquinoline alkaloids: Characterization of drug-cell interaction.
AU Ma J.Y.C.; Barger M.W.; Ma J.K.H.; Castranova V.
SO EXP. LUNG RES., (1992) 18/6 (829-843).
ISSN: 0190-2148 CODEN: EXLRDA

AB The objective of this study was to investigate the effects of various bisbenzylisoquinoline (BBIQ) alkaloids on respiratory burst activity of alveolar macrophages and to characterize the interaction of these drugs with alveolar phagocytes. BBIQ alkaloids were chosen for study because they exhibit a wide range of antifibrotic potencies in a rat model,

with tetradrine being very effective and tubocurarine being ineffective. These drugs inhibited zymosan-stimulated oxygen consumption with a potency sequence of tetradrine (TT) .apprx. fangchinoline (FA) > berbamine (BE) .apprx. cepharanthine (CE) .apprx. cycleanine (CY) >> tubocurarine (TU). This inhibition of respiratory burst activity could not be attributed to a drug-induced decline in the ATP content of these pneumocytes. Drug binding to alveolar macrophages was directly dependent on temperature and drug concentration. The sequence for binding capacity was FA > TT .apprx. BE .apprx. CY > CE >> TU. Therefore, there was no simple relationship between binding capacity and inhibitory potency. Binding capacity was not related to lipophilicity of these alkaloids. In addition, tetradrine failed to bind to metabolically dead cells or sonicated macrophage preparations. These data suggest that the interaction of BBIQ alkaloids with phagocytes is not simply nonspecific binding to membrane lipids. Alteration of the cytoskeletal system with vinblastine, taxol, or cytochalasin B decreased tetradrine binding by approximately 33% when added separately and by 93% when added jointly. Pre-exposure of alveolar macrophages to stimulants increased the ability of BBIQ alkaloids to inhibit both oxygen consumption and superoxide release. These data suggest that the mechanism by which BBIQ alkaloids inhibit activation of phagocytes involves microtubules and bules and microfilaments. Pre-exposure of macrophages to stimulants would change the conformation of cytoskeletal components and may make these structures more susceptible to drug interaction.

✓ L27

ANSWER 16 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

AN 92142065 EMBASE

TI Effects of ibogaine on acute signs of morphine withdrawal in rats: Independence from tremor.

AU Glick S.D.; Rossman K.; Rao N.C.; Maisonneuve I.M.; Carlson J.N.
SO NEUROPHARMACOLOGY, (1992) 31/5 (497-500).

ISSN: 0028-3908 CODEN: NEPHBW

AB Because of the claim that ibogaine suppresses the symptoms

of 'narcotic withdrawal' in humans,

the effect of ibogaine on naltraxone-precipitated

withdrawal signs in morphine-dependent rats was assessed. Morphine

was administered subcutaneously through implanted silicone

reservoirs for 5 days. Ibogaine (20, 40 or 80 mg/kg, i.p.)

or saline was administered 30 min prior to challenge with naltraxone (1 mg/kg, i.p.) and withdrawal signs were counted for the following

2 hr. Ibogaine (40 and 80 mg/kg) significantly reduced the

occurrence of four signs (wet-dog shakes, grooming, teeth chattering and diarrhea) during naltraxone-precipitated withdrawal: three other signs (weight loss, burying and flinching) were unaffected.

Ibogaine induces head and body tremors lasting for 2-3 hr

and the tremors might have interfered with the expression of opioid withdrawal. To examine this issue, another experiment was conducted

in which ibogaine (40 mg/kg) or saline was administered 4 hr prior to challenge with naltraxone. Although there was a complete absence of tremors, ibogaine still significantly reduced

the occurrence of the same four signs of withdrawal.

- ✓L27 ANSWER 17 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 7
AN 92:345251 BIOSIS
TI THE INFLUENCE OF CHRONIC NICOTINE TREATMENT ON
AU STRESS-INDUCED ULCERATION AND EMPTYING RATE IN RATS.
QIU B S; CHO C H; OGLE C W
SO EXPERIENTIA (BASEL) 48 (4). 1992. 389-391. CODEN: EXPEAM ISSN:
0014-4754
AB Ten-day treatment with nicotine (5, 25 or 50 .mu.g/ml
drinking water) dose-dependently intensified
gastric ulceration induced by cold-resistant, and emptying rate.
Stomach contractions produced by graded doses of bethanechol i.v.
were elevated further by nicotine treatment. It is
suggested that chronic nicotine administration produces
hypersensitivity of the gastric muscarinic receptors; stomach
hypermotility contributes to the ulcer-worsening action of the
alkaloid.

- ✓L27 ANSWER 18 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 8
AN 93:190556 BIOSIS
TI EFFECTS OF IBOGAINE ON NALOXONE-PRECIPITATED WITHDRAWAL IN
MORPHINE-DEPENDENT MICE.
AU FRANCES B; GOUT R; CROS J; ZAJAC J M
SO FUNDAM CLIN PHARMACOL 6 (8-9). 1992. 327-332. CODEN: FCPHEZ
AB In naive mice, ibogaine at a tremorigenic dose (30
mg/kg, ip), did not produce antinociception but did potentiate the
antinociceptive potency of morphine in the tail-flick test. In
morphine-dependent mice, ibogaine did not eliminate
withdrawal symptoms but significantly increased the number of
repetitive vertical jumps induced by naloxone, whatever the duration
of the chronic morphine treatment. By comparison,
repetitive jumping induced by .alpha.-naphthoxyacetic acid
(.alpha.-NOAA), a non-convulsant drug which induced jumping without
affecting other morphine-withdrawal signs, was not significantly
modified by ibogaine. These results indicate that while
acute antinociceptive effects of morphine are modulated by
ibogaine, this drug, shown to alleviate opiate dependence in
man, does not attenuate in mice opioid withdrawal manifestations.

- ✓L27 ANSWER 19 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 9
AN 93:57783 BIOSIS
TI IMMUNOLOGICAL EFFECT OF COCAINE AND HOST RESISTANCE IN MICE.
AU PACIFICI R; AVICO U; BELOGI L; BORELLI G; CROCE C; DI CARLO S;
PICHINI S; SANTIANGELI C; ZUCCARO P; TUBARO E
SO INT J IMMUNOTHER 8 (2). 1992. 91-99. CODEN: IJIMET ISSN: 0255-9625
AB A potential role of drugs of abuse, especially
morphine, cocaine and alcohol, as co-factors in the development of
infections and diseases has been suggested. To better understand the
immune system function in cocaine-abuse cases, several immunological
parameters were examined in mice. As blood-borne cellular host
defences are exposed to cocaine during episodes of cocaine use, the
effect of cocaine was investigated on murine polymorphonuclear

leukocyte (PMNL) microbicidal function, lymphocyte natural killer cell cytotoxicity and responsiveness of lymphocytes to mitogen. Resistance to Candida albicans infection and to implantation and growth of several tumours was also studied. T-cell responses to mitogen PHA and cytotoxic activity of immune spleen cells were found to be depressed in mice dosed with 5 mg/kg of cocaine. An enhancement of PMN phagocytosis and killing properties by cocaine was observed. A lack of negative influence of cocaine treatment on resistance to infections and implantation of tumours was also found. The response to cocaine varied not only with the dose administered but also with the duration of treatment. This observation, pointing to a possible role of this alkaloid drug in the particular mechanisms of immune cell regulation, may be important to understand a number of normal and abnormal biological processes caused by cocaine itself.

✓L27 ANSWER 20 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 10
 AN 92:239080 BIOSIS
 TI TREATMENT OF CRACK COCAINE USE WITH CARBAMAZEPINE.
 AU HALIKAS J A; KUHN K L; CREA F S; CARLSON G A; CROSBY R
 SO AM J DRUG ALCOHOL ABUSE 18 (1). 1992. 45-56. CODEN: AJDABD ISSN: 0095-2990

AB Crack is a rock crystalline alkaloid form of cocaine which can be smoked. At the University of Minnesota, we have developed an experimental pharmacologic treatment for cocaine abusers. Of 26 patients treated to date, 16 have been crack cocaine users. During the hundred days preceding treatment, the 16 crack subjects used cocaine by all routes on average of 71 days each. Improvement was based on a self-reported decrease in cocaine frequency of use. Using carbamazepine, seven highly successful and six partially successful patients reduced their use to 0.7 days and 26 days per 100 days, respectively. These results, though hopeful, must be viewed with caution and considered preliminary and tentative.

✓L27 ANSWER 21 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
 AN 92118874 EMBASE
 TI [Uses and abuses of Ipecacuana syrup: A review].
 AU USOS Y ABUSOS DEL JARABE DE IPECACUANA: REVISION.
 AU Villalba Bedoya D.; Agudo Martinez M.A.; Chavernas Bustamante S.;
 SO Valverde Molina E.; Ortega de la Cruz C.
 FARM. CLIN., (1992) 9/1 (42-54).
 ISSN: 0212-6583 CODEN: FACLE2

AB The ipecacuana or ipecac is an American bush from the roots of which a powder is obtained for use in the preparation of pharmaceutical products. Amongst its therapeutic applications we may single out its antiepileptic, emetic and expectorant properties, due mainly to the presence of its majority alkaloids: emetine and cephalin. At the present time its use is restricted, in syrup form, as an emetic for the treatment of intoxications taking place orally. In this study we review the information available in the literature, we describe the galenic formulations contained in the different pharmacopoeias, dosage regimens in children and adults, as well as the precautions,

contraindications, interactions and adverse reactions. We also describe the accidental intoxications caused by the mistaken administration of the fluid extract instead of the syrup, and chronic ipecacuanha syrup intoxications whether involuntary or intentional (Munchausen Syndrome by proxy). We also set forth the rules for the patient's education and information in order to prevent possible intoxications due to the misuse of ipecacuanha syrup.

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ANSWER 22 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

93074635 EMBASE

Pharmacological aspects of drug induced headache.

Cankat Tulunay F.

FUNCT. NEUROL., (1992) 7/6 SUPPL. (15-16).

ISSN: 0393-5264 CODEN: FUNEE6

Patients with recurrent headache often describe a history that includes frequent use of medications, such as analgesics, barbiturates, benzodiazepines, opiates, caffeine, ergot derivatives or their combinations. Because many diverse substances may be abused in headache patients, the causes and mechanisms may be different. The mechanism of drug-induced headache is not known. There is evidence to suggest that drug-induced headache may be restricted to those with primary headache disorders, especially migraineurs.

✓L27
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ANSWER 23 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

92089916 EMBASE

[Tetrahydroisoquinolines - Endogenous products after chronic alcohol abuse].

TETRAHYDROISOCHINOLINE - ENDOGENE PRODUKTE NACH CHRONISCHEM ALKOHOLMISSBRAUCH.

Haber H.; Melzig M.

PHARMAZIE, (1992) 47/1 (3-7).

ISSN: 0031-7144 CODEN: PHARAT

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ANSWER 24 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 11

92:7434 BIOSIS

MULTIDRUG RESISTANCE OF MALIGNANT TUMORS.

BAK M

ORV HETIL 132 (40). 1991. 2187-2192. CODEN: ORHEAG ISSN: 0030-6002
The development of resistance to chemotherapy is a major problem in the treatment of malignant tumors. Clinically, this is characterized by short periods of remission and failure to respond to subsequent therapy. Multidrug-resistance or pleiotropic resistance describes the simultaneous expression of cellular resistance to a wide range of structurally unrelated drugs (e.g. alkaloids, anthracyclines, antibiotics, etc.). The most frequently reported alteration of multidrug-resistant cells is the overexpression of a 170 kD glycoprotein (P-170 or P-glycoprotein) encoding by the MDR gene family. A great deal of evidence has suggested that the P-glycoprotein is, in fact, an energy-dependent drug efflux pump. Pharmacological overcome of MDR may indicate to circumvent clinically observed drug

resistance.

✓L27 ANSWER 25 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS. DUPLICATE 12

AN 91:532972 BIOSIS

TI DRUG ABUSE AND HEADACHE.

AU ELKIND A H

SO MED CLIN NORTH AM 75 (3). 1991. 717-732. CODEN: MCNAA9 ISSN: 0025-7125

✓L27 ANSWER 26 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS. DUPLICATE 13

AN 92:30081 BIOSIS

TI INDUCTION OF MULTIPLE-DRUG RESISTANCE DURING ANTI-NEOPLASTIC CHEMOTHERAPY IN-VITRO.

AU LICHT T; FIEBIG H-H; BROSS K J; HERRMANN F; BERGER D P; SHOEMAKER R; MERTELSMANN R

SO INT J CANCER 49 (4). 1991. 630-637. CODEN: IJCNAA ISSN: 0020-7136

AB Induction of P-glycoprotein-related multi-drug-resistance (MDR) has been shown in normal and malignant tissues to result from environmental stresses such as heat shock, exposure to carcinogens or X-ray irradiation. To identify conditions under which MDR is enhanced during anti-neoplastic chemotherapy, a cell line showing low-level intrinsic MDR was investigated. In the pleural mesothelioma cell line, PXF1118, < 1% of cells expressed P-glycoprotein (P-gp), as shown by immunocytochemical staining with monoclonal antibody (MAB) MRK16. Exposure of PXF1118 to vincristine, vindesine, vinblastine or doxorubicin for 2-3 weeks led to an increase in the MDR cell fraction of up to 15-28% during 2 to 3 weeks. For doxorubicin and vindesine, dose-dependence was observed: drug concentrations not capable of eliciting cytotoxicity failed to induce significant P-gp expression. Nutrient starvation in aging medium, exposure to activated cyclophosphamide (even at high concentrations) or cisplatin caused only negligible MDR induction. After exposure to vindesine for 6 weeks, tumor colonies exhibited highly enhanced resistance to Vinca alkaloids, doxorubicin, etoposide and decarbazine, whereas their sensitivity to mitomycin, activated cyclophosphamide or cisplatin remained unchanged. As determined by [³H]-thymidine uptake and proliferation antigen expression, induction of MDR phenotype was observed at minimal proliferative activity with no change in cell count during exposure to anti-cancer drugs, thus suggesting that the drug treatments changed the phenotype of the cells rather than selecting for a resistant sub-population. In addition, changes in cell differentiation were observed during MDR induction. Induction of P-gp during exposure to anti-cancer drugs thus provides a model for MDR development during initially successful chemotherapy.

✓L27 ANSWER 27 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

AN 91337887 EMBASE

TI Is multidrug resistance relevant in breast cancer?.

AU Wishart G.C.; Kaye S.B.

SO EUR. J. SURG. ONCOL., (1991) 17/5 (485-488).

ISSN: 0748-7983 CODEN: EJSOE7

AB The multidrug resistance phenotype is associated with expression of P-glycoprotein (P-gp) an energy-dependent drug

efflux pump. P-gp is expressed in several clinically resistant human cancers. This article discusses the evidence that P-gp expression may be implicated in the development of clinical drug resistance in patients with breast cancer.

- ✓ L27 ANSWER 28 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
AN 91081620 EMBASE
TI Keynote address: Multidrug resistance: A pleiotropic response to cytotoxic drugs.
AU Fairchild C.R.; Cowan K.H.
SO INT. J. RADIAT. ONCOL. BIOL. PHYS., (1991) 20/2 (361-367).
ISSN: 0360-3016 CODEN: IOBPD3
AB Tumor cells exposed in tissue culture to one of several different classes of antineoplastic agents, including anthracyclines, vinca alkaloids, epipodophyllotoxins, and certain antitumor antibiotics, can develop resistance to the selecting agent and cross resistance to the other classes of agents. This phenomena of multidrug resistance is generally associated with decreased drug accumulation and overexpression of a membrane glycoprotein. This membrane protein, referred to as P-glycoprotein, apparently acts as an energy-dependent drug efflux pump. Multidrug resistance in human MCF-7 breast cancer cells selected for resistance to adriamycin (AdR MCF-7) is associated with amplification and overexpression of the mdrl gene which encodes P-glycoprotein. A number of other changes are also seen in this resistant cell line including alterations in Phase I and Phase II drug metabolizing enzymes. Similar biochemical changes occur in a rat model for hepatocellular carcinogenesis and are associated in that system with broad spectrum resistance to hepatotoxins. The similar changes in these two models of resistance suggests that these changes might be part of a battery of genes whose expression can be altered in response to cytotoxic stress, thus rendering the cell resistant to a wide variety of cytotoxic agents.

- ✓ L27 ANSWER 29 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 14
AN 91:138855 BIOSIS
TI ANTITUMOR ACTIVITIES OF IKP-104 A 4-1H PYRIDIZINONE DERIVATIVE ON CULTURED AND IMPLANTED TUMORS.
AU MIZUHASHI F; MURATA K; KIKAGAKI T; NEZU M; SANO M; TOMITA I
SO JPN J CANCER RES 81 (12). 1990. 1300-1306. CODEN: JJCREP ISSN: 0910-5050
AB Antitumor activities of IKP-104, a 4(1H)-pyridazinone derivative, were investigated with cultured tumor cell lines and implanted tumors in mice. IKP-104 inhibited the growth of cultured murine tumor cell lines (L1210 leukemia, Lewis lung carcinoma and B16 melanoma) and human tumor cell lines (K562 leukemia and HeLa cervical carcinoma). It also had antitumor effects on implanted murine ascitic tumors (L1210 leukemia and sarcoma 180) and a murine solid tumor (Lewis lung carcinoma). IKP-104 could be classified as a phase-dependent cytostatic drug based on the mode of growth inhibition of cultured B16 melanoma cells compared with those of several other antitumor agents. The effect of IKP-104 on the cell cycle traverse of cultured B16 melanoma cells was estimated by morphological and flow

cytometric analyses. Cells accumulated in the mitotic phase, and abortive mitosis or polyploidy or multinucleation was induced from 6 h after exposure to IKP-104. Based on these results, IKP-104 is expected to be useful for the treatment of tumors, and its mode of action seemed to be similar to that of metaphase arrestants such as colchicine or vinca alkaloids.

✓L27

AN 91010751 EMBASE
TI Effects of cathinone and amphetamine on the neurochemistry of dopamine in vivo.

AU Pehek E.; Schetchter M.D.; Yamamoto B.K.
SO NEUROPHARMACOLOGY, (1990) 29/12 (1171-1176).

ISSN: 0028-3908 CODEN: NEPHBW

AB The effects of (-)-cathinone, the primary psychoactive alkaloid of the Khat plant, were compared to those of (+)amphetamine in the anterior caudate-putamen and the nucleus accumbens. In vivo microdialysis was used to measure extracellular levels of dopamine and metabolites in both regions of the brain simultaneously, after intraperitoneal administration of 0.8, 1.6 or 3.2 mg/kg of either drug (doses expressed as the salts). Both drugs increased levels of dopamine but decreased levels of metabolites in a dose-dependent manner. However, the relative magnitude of these effects depended upon the specific drug, the dose and area of the brain examined. At the largest dose used, amphetamine had a relatively greater effect than cathinone on dopamine in both caudate and accumbens. However, among smaller doses, this difference was only observed in the nucleus accumbens after administration of 1.6 mg/kg. The results also demonstrated a differential regional effect of both drugs at 3.2 mg/kg, in that both had a greater effect on dopamine in the caudate, as opposed to the accumbens. These findings demonstrate a functional heterogeneity of the striatum of the rat, that may be relevant to the understanding of both normal brain function and the neural responses to psychoactive drugs.

✓L27

AN 91085356 EMBASE
TI Pharmacological properties of the stimulant khat.

AU Kalix P.
SO PHARMACOL. THER., (1990) 48/3 (397-416).

ISSN: 0163-7258 CODEN: PTHTDT

AB The chewing of the stimulant leaf khat is a habit that is widespread in certain countries of East Africa and the Arabian peninsula. During the last decade, important progress has been made in understanding the pharmacological basis for the effects of khat. It is now known that the CNS action of this drug is due to the presence of the alkaloid cathinone, and the results of various in vitro and in vivo experiments indicate that this substance must be considered a natural amphetamine. It is the purpose of the present review to describe briefly the khat habit and to summarize the pharmacology of khat and of its active constituents.

✓L27 ANSWER 32 OF 104 MEDLINE

AN 92202110 MEDLINE

TI Multidrug resistance: a transport system of antitumor agents and xenobiotics.

AU Tsuruo T

SO Princess Takamatsu Symp, (1990) 21 241-51. Ref: 42

Journal code: HHI.

AB Resistance of tumors to a variety of chemotherapeutic agents presents a major problem in cancer treatment. Resistance to such agents as doxorubicin, Vinca alkaloids, and actinomycin D can be acquired by tumor cells after treatment with a single drug. The gene responsible for multidrug resistance, termed *mdr1*, encodes a membrane glycoprotein (P-glycoprotein) that acts as a pump to transport various cytotoxic agents including various xenobiotics out of the cell. The amount of P-glycoprotein expression has been measured in tumor samples and was found to be elevated in intrinsically drug-resistant cancers of the colon, kidney, and adrenal as well as in some tumors that acquired drug***-morphine interaction as well as to det. if

resistance after chemotherapy. The protein was also found to be elevated in cells treated with xenobiotics. P-glycoprotein has been shown to bind anticancer drugs and several resistance-reversing agents including calcium channel blockers, and to be an ATPase. We recently reconstituted the purified P-glycoprotein into artificial liposomes. Reconstituted P-glycoprotein showed ATPase activity, ATP-dependent drug-transport activity, and calcium channel blocker-binding activity. This model provides many advantages for studies of the biochemical functions of P-glycoprotein. In addition to these basic interests, the protein is of considerable interest as a target for cancer chemotherapy because it appears to be involved in both acquired multidrug resistance and intrinsic drug resistance in human cancer. The selective killing of tumor cells expressing P-glycoprotein could be very important in future cancer therapy.

✓L27 ANSWER 33 OF 104 MEDLINE

AN 90031407 MEDLINE

TI Pharmacotherapy for smoking cessation.

AU Nunn-Thompson CL; Simon PA

SO Clin Pharm, (1989 Oct) 8 (10) 710-20. Ref: 63

Journal code: DKC. ISSN: 0278-2677.

AB Nicotine dependence and the role of various

pharmacotherapeutic adjuncts in the medical management of nicotine withdrawal and smoking cessation are reviewed. Nicotine has been shown to be the drug in tobacco that causes addiction. The nicotine withdrawal syndrome is primarily characterized by craving, irritability, frustration, anger, anxiety, poor concentration, restlessness, weight gain, and decreased heart rate.

Pharmacotherapeutic interventions can be classified into four groups: therapy that (1) replaces nicotine, (2) antagonizes nicotine, (3) provides symptomatic treatment

for nicotine withdrawal, and (4) deters smoking. Nicotine replacement therapy with nicotine polacrilex gum has had minimal effect on increasing-smoking cessation among patients seen in a general medical practice setting. It is most effective in nicotine dependent smokers when it is used concomitantly with behavioral or psychological counseling. Nicotine antagonist therapy with mecamylamine may be useful in recalcitrant cases of nicotine dependence. Clonidine, in both oral and transdermal forms, has been shown to be effective for reduction of symptoms and craving associated with smoking cessation. Research on using the tricyclic antidepressants imipramine and doxepin to promote smoking cessation by reducing withdrawal symptoms is in its preliminary phases. Lobeline, an alkaloid with effects similar to those of nicotine, is an FDA Category III drug (i.e., safe, but of unknown efficacy) and is available without prescription. Silver acetate chewing gum deters smoking by producing an unpleasant metallic taste on concomitant ingestion of the agent and tobacco. It is an FDA Category III drug and is available without prescription. Drugs used in therapy of nicotine withdrawal include nicotine replacements, nicotine antagonists, agents to lessen the symptoms of withdrawal, and smoking deterrents. None of the drugs is completely effective. Successful drug use for smoking cessation involves consideration of the psychological, as well as physiological, aspects of nicotine addiction.

L27
AN 90175204 MEDLINE
TI Heterocycles as physiological ligands for the benzodiazepine receptor and for other binding sites.
AU Wildmann J
SO Pharmacol Res, (1989 Nov-Dec) 21 (6) 673-82. Ref: 26
AB Recently pharmacologically active benzodiazepines, including diazepam, have been identified in common foodstuffs, e.g. wheat and potato. The chronic intake by way of plant food may explain the existence of benzodiazepines in the brain and in other tissues of various mammals and man. Hitherto these alkaloid-like compounds were considered to be merely products of industrial synthesis. All the benzodiazepines used in therapy show a similar chemical structure. However, depending on particular substituents, agonistic benzodiazepines can be subdivided into groups of different pharmacological potency. Besides benzodiazepines, in the past years other alkaloid drugs, e.g. derivatives of morphine, norharmane and tetrahydronorharmane, have been isolated from animals. Some of these substances have been discussed as physiological ligands of specific neuronal binding sites. Indications have been provided that at least part of these compounds or their precursors may be of plant origin too. The presence of these compounds in plants used for food may suggest complex interactions between plant and animal, exceeding the nutritional aspect.

DUPLICATE 15

- ✓ L27 ANSWER 35 OF 104 MEDLINE
 AN 89317073 MEDLINE
 TI [Cerebrovascular accidents in relation to drug consumption or drug abuse].
 Accidents vasculaires cerebraux en relation avec la prise de medicaments ou de drogues.
 AU Uldry PA; Regli F
 SO Schweiz Rundsch Med Prax, (1989 Jun 6) 78 (23) 663-6. Ref: 41
 Journal code: SRM. ISSN: 0369-8394.
 AB Many drugs may cause cerebral infarction or hemorrhage. The authors describe the epidemiology and the physiopathological aspects of stroke in patients using anticoagulant therapy, oral contraception or ergot alkaloids. Cerebrovascular complications are also noticed in abusers of cocaine or other stimulants of the central nervous system: amphetamine, phenylpropanolamine, xanthines.
- ✓ L27 ANSWER 36 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 16
 AN 90:91017 BIOSIS
 TI COMPARATIVE EFFECTS OF FAGARONINE ADRIAMYCIN AND ACLACINOMYCIN ON K562 CELL SENSITIVITY TO NATURAL-KILLER-MEDIATED LYSIS LACK OF AGREEMENT BETWEEN ALTERATION OF TRANSFERRIN RECEPTOR AND CD15 ANTIGEN EXPRESSIONS AND INDUCTION OF RESISTANCE TO NATURAL KILLER.
 AU BENOIST H; COMOE L; JOLY P; CARPENTIER Y; DESPLACES A; DUFER J
 SO CANCER IMMUNOL IMMUNOTHER 30 (5). 1989. 289-294. CODEN: CIIMDN ISSN: 0340-7004
 AB Little is known about membrane target antigens for natural killer (NK) cells. Transferrin receptor and CD15 antigen might be two of these target structures. A novel antileukemic alkaloid, fagaronine, is able to induce hemoglobin synthesis in the K562 cell line. Numerous reports suggest relations between the expression of natural killer target structures and the differentiation stage of malignant cells. Effects of fagaronine on the expression of glycophorin A, transferrin receptor and CD15 antigen and susceptibility to NK-mediated lysis have been investigated in K562 cells and compared to those of two anthracyclines (Adriamycin and aclacinomycin A) known to be erythroid-differentiation inducers. When comparing the balance of differentiating effect and toxicity, the dose and time-dependent effects of the drugs, fagaronine and aclacinomycin, are equivalent on K562 cells. In experimental conditions where fagaronine (3500 nM), Adriamycin (40 nM) and aclacinomycin (15 nM) recruit the same percentage of hemoglobin-containing cells (40%-50%), glycophorin A expression increases and transferrin receptor expression decreases. Only Adriamycin treatment decreases CD15 antigen expression. In addition, Adriamycin and aclacinomycin, but not fagaronine, induce resistance to NK-mediated lysis. These data suggest that (a) it is unlikely that CD15 antigen and transferrin receptor, separately considered, can be unique target structures for NK cells; and (b) fagaronine is a potent erythroid inducer which, in our system, has similar effects as aclacinomycin without induced resistance to NK attack.

✓L27 ANSWER 37 OF 104 MEDLINE

AN 89196428 MEDLINE

TI Preparation of low density lipoprotein-9-methoxy-ellipticin complex and its cytotoxic effect against L1210 and P 388 leukemic cells in vitro.

AU Samadi-Baboli M; Favre G; Blancy E; Soula G

SO Eur J Cancer Clin Oncol, (1989 Feb) 25 (2) 233-41.

Journal code: ENW. ISSN: 0277-5379.

AB Previous studies have suggested that low density lipoprotein (LDL) may be used as a drug targeting carrier for chemotherapeutic agents to neoplastic cells. In this study the cytotoxic agent 9-methoxy-ellipticin (MeOE) was incorporated into dimyristoyl phosphatidylcholine, cholesterol oleate stabilized microemulsion and the latter fused with human LDL. Both agarose electrophoresis migration and the electron microscopic shape of the drug-LDL complexes were similar to those of native LDL. The in vitro cytotoxic tests on L1210 and P388 leukemic cells demonstrated that the complex was able to kill cells and was more effective than the free drug. This cytotoxic activity of the drug -LDL complex depends on the LDL high affinity receptor: the native LDL reduces the killing power. In contrast, methylated LDL, which does not bind to the LDL receptor, has no effect on it. On the other hand, heparin, which prevents binding on the cell surface receptors, partially reduced the cytotoxic activity of the drug-lipoprotein complex. These results suggest that it is possible to incorporate lipophilic cytotoxic drugs into LDL, using a technique of fusion with the microemulsion which contains the drug. This technique allows us to obtain a drug-LDL complex which is able to kill cells via the LDL receptor pathway.

✓L27 ANSWER 38 OF 104 MEDLINE

AN 89228773 MEDLINE

TI In vitro evaluation of mismatched double-stranded RNA (ampligen) for combination therapy in the treatment of acquired immunodeficiency syndrome.

AU Montefiori DC; Robinson WE Jr; Mitchell WM

SO AIDS Res Hum Retroviruses, (1989 Apr) 5 (2) 193-203.

Journal code: ART. ISSN: 0889-2229.

AB Multiple drug effect analyses with mismatched double-stranded RNA (mismatched dsRNA or Ampligen) as a core drug were performed to identify other agents and mechanisms through which mismatched dsRNA may potentiate effective therapeutic intervention in human immunodeficiency virus (HIV) infection. Antiviral activities were defined by a microtiter infection assay utilizing MT-2 cells as targets and HTLV-III-B produced in H9 cells as a virus source. The scope of agents tested included rIFN-alpha A, rIFN-beta Ser 17, and rIFN-gamma as cytokines; azidothymidine and phosphonoformate (Foscarnet) as inhibitors of reverse transcription; ribavirin as a putative inhibitor of proper HIV mRNA capping; amphotericin B as a lipophile; and castanospermine as a glycoprotein processing (glucosidase I) inhibitor. Separately, each drug demonstrated dose-dependent anti-HIV activity and, when.

used in combination with mismatched dsRNA, demonstrated synergism. Although mismatched dsRNA was synergistic with all three IFNs for anti-HIV activity in microtiter infection assays, it did not potentiate the transient inhibition of virus production observed for IFN in cultures of H9/HTLV-III-B cells. The results of these studies suggest that the pleiotropic activities of dsRNAs differ from those of IFN and may provide synergism in combination therapy with a wide range of antiviral drugs for the treatment of the acquired immunodeficiency syndrome (AIDS).

✓L27
AN
TI
AU
SO

ANSWER 39 OF 104 MEDLINE
89098663 MEDLINE
Ergotism masquerading as arteritis.
Tarnower A; Alguire P
Postgrad Med, (1989 Jan) 85 (1) 103-4, 107-8.
Journal code: PFK. ISSN: 0032-5481.

L27
AN
TI
AU
SO
AB

ANSWER 40 OF 104 MEDLINE
89063245 MEDLINE
Effects of homoharringtonine on protein glycosylation in human bladder carcinoma cell T-24.
Ling YH; Tseng MT; Harty JI
Cancer Res, (1989 Jan 1) 49 (1) 76-80.
Journal code: CNF. ISSN: 0008-5472.

Rates of [³H]glucosamine and mannose incorporation into glycoproteins and dolichol-linked oligosaccharides in exponentially growing T-24 bladder cancer cells were examined after exposure to homoharringtonine (HHT). Two-h treatment of HHT (10 ng/ml) reduced [³H]glucosamine and mannose incorporation into the glycoproteins to 61% and 32% of controls. Concomitantly, respective sugar incorporation into dolichol-linked oligosaccharides was elevated 29% and 30% above control. The maximal inhibition of glycoprotein biosynthesis and stimulation of the lipid-linked oligosaccharides occurred within 2 to 4 h after exposure to 50 ng/ml of the drug. Prolonged drug exposure (greater than 8 h) resulted in generalized suppression of glycoprotein biosynthesis and lipid-linked oligosaccharide formation. The kinetic study indicated that the time course on reduction of glycoprotein biosynthesis and accumulation of dolichol-linked oligosaccharides paralleled the decline in protein synthesis. Further, the inhibition of glycoprotein synthesis and stimulation of dolichol-linked oligosaccharides were reversible 4 h after drug withdrawal. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis autoradiographic analysis of the [³H]mannose-labeled glycoprotein revealed no pronounced difference between HHT-treated and control cells. These data suggest that the inhibition of glycosylation results from combined decrease of acceptors for glycoprotein biosynthesis with a simultaneous accumulation of the dolichol-linked oligosaccharides. Collectively these data may account for many of the HHT-induced bioresponses.

✓L27
AN

ANSWER 41 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS
89:188038 BIOSIS

TI

ANALGESIC-INDUCED CHRONIC HEADACHE LONG-TERM RESULTS OF WITHDRAWAL THERAPY.

AU
SO
AB

DIENER H-C; DICHGANS J; SCHOLZ E; GIESELHART S; GERBER W-D; BILLE A
J NEUROL 236 (1). 1989. 9-14. CODEN: JNRYA9 ISSN: 0340-5354
Headache characteristics are described in 139 patients with chronic
daily or almost daily headaches due to regular intake of analgesics
and the short- and long-term results of drug
withdrawal. Drug-induced headache was described as
dull, diffuse, and band-like, and usually started in the early
morning. The mean duration of the original headache (migraine or
tension headache) was 25 years; regular intake of drugs and chronic
daily headache had started 10 and 6 years prior to withdrawal
therapy, respectively. Patients took an average of 34.6
tablets or analgesic suppositories or antimigraine drugs per week
containing 5.8 different substances. The drugs most often used were
caffeine (95%), ergotalkaloids (89%), barbiturates (64%), and
spasmolytics, paracetamol, and pyrazolone derivatives (45%-46%). A
total of 103 patients (68 migraine, 35 tension or combination
headache) were available for interviews at a mean time interval of
2.9 years after an inpatient drug withdrawal programme. Chronic
headache had disappeared or was reduced by more than 50% in
two-thirds of patients. Positive predictors for successful
treatment were migraine as primary headache, chronic headache
lasting less than 10 years, and regular intake of ergotamine. Drug
intake was significantly reduced and patients used single substances
more often. Patients who originally suffered from migraine,
superimposed on the daily headache, also experienced a significant
improvement in the frequency of the migraines and their intensity.
Migraine prophylaxis through beta-blocking agents and calcium channel
antagonists was more efficient after drug-
withdrawal therapy.

✓L27

AN 89:52808 BIOSIS

ANSWER 42 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 17

TI INCREASED MDR GENE EXPRESSION AND DECREASED DRUG ACCUMULATION IN
MULTIDRUG-RESISTANT HUMAN MELANOMA CELLS.

AU
SO
AB

LEMONTT J F; AZZARIA M; GROS P
CANCER RES 48 (22). 1988. 6348-6353. CODEN: CNREA8 ISSN: 0008-5472
Multidrug-resistant clones of a drug-sensitive human malignant
melanoma cell line were isolated by single-step selection in culture
medium containing either vincristine (4.5 ng/ml or 7.5 ng/ml),
vinblastine (3 ng/ml), or colchicine (8 ng/ml). This protocol yielded
primary colonies showing relatively low (4- to 24-fold) levels of
drug resistance. These clones exhibit the classical multidrug
resistance (MDR) phenotype, being cross-resistant to Vinca
alkaloids, anthracyclines, colchicine, and actinomycin D.
The appearance of an MDR phenotype in these cells was linked to a
decreased accumulation and increased efflux of the drug
[3H]vinblastine when compared to the drug-sensitive melanoma cell
line. This increased drug efflux was dependent on
the presence of cellular ATP and could be reduced by
treatment of the cells with rotenone and deoxyglucose. A
partial human mdr complementary DNA clone was used to monitor the

degree of amplification and the level of transcription of this gene in the cloned lines. All 5 MDR sublines expressed increased levels of the specific 4.5-kilobase *mdr* mRNA, but did not show *mdr* gene amplification. Our results indicate that relatively low levels of drug resistance, similar to those observed clinically and in experimental xenografts, can be achieved by single-step drug selection and result from increased expression of at least one member of the *mdr* gene family.

L27
AN 88:484655 BIOSIS
TI THE CARBOXYLIC IONOPHORE MONENSIN INHIBITS ACTIVE DRUG EFFLUX AND MODULATES IN-VITRO RESISTANCE IN DAUNORUBICIN RESISTANT EHRlich ASCITES TUMOR CELLS.
AU SEHESTED M; SKOVSGAARD T; ROED H
SO BIOCHEM PHARMACOL 37 (17). 1988. 3305-3310. CODEN: BCPA6 ISSN: 0006-2952

AB Acquired cellular resistance of anthracycline and vinca alkaloid drugs (pleiotropic resistance) is commonly associated with reduced drug accumulation, a phenomenon which is thought to be partly due to increased energy-dependent drug efflux. We have previously detected increased plasma membrane traffic to, and content of, the acid endosomal compartment in pleiotropic resistant Ehrlich ascites and P388 leukemia cells. This suggested that the endosome could be associated with the pleiotropic resistance phenotype by a mechanism of vesicular drug trapping and transport. The present study was undertaken in order to test the effects of the carboxylic ionophores monensin and nigericin, which are known to both disrupt intracellular vesicular traffic and to raise intravesicular pH, with relation to the pleiotropic resistance phenotype. Both monensin and nigericin increased daunorubicin (DNR) accumulation in daunorubicin resistant Ehrlich ascites tumor cells (EHR2/DNR+) in a dose-dependent manner. Further, monensin inhibited glucose induced DNR efflux from EHR2/DNR+ cells loaded with drug by energy deprivation. On the other hand, monensin had only negligible effect on DNR accumulation and efflux in wild-type Ehrlich ascites tumor cells (EHR2). In a clonogenic assay system, monensin reduced resistance to DNR in EHR2/DNR+, whereas only an additive effect was obtained in EHR2. However, both ionophores proved too toxic in in vivo experiments. These results, showing that drugs known to disrupt endosomal functions also inhibit the pleiotropic resistance phenotype, support the suggested link between the endosome and pleiotropic resistance.

L27
AN 89178814 MEDLINE
TI Khat: a plant with amphetamine effects [see comments].
AU Kalix P
SO J Subst Abuse Treat, (1988) 5 (3) 163-9. Ref: 50
Journal code: KAI. ISSN: 0740-5472.

AB The chewing of leaves of the khat shrub is common in certain countries of East Africa and the Arabian peninsula, and some khat users are subject to psychic dependence on this stimulant. Recently,

important progress has been made in understanding the pharmacological basis for the effects of khat. It is now known that the CNS stimulation is mainly due to the presence of the alkaloid cathinone in the leaves, and the results of various in vitro and in vivo experiments indicate that this substance must be considered a "natural amphetamine." In recent years, several cases of khat intoxication observed in the USA and in Great Britain have been described in the literature. In view of these developments, the khat habit and its health effects are described, and the possibilities for the treatment of acute khat intoxication are discussed.

✓ L27 ANSWER 45 OF 104 MEDLINE
AN 88333886 MEDLINE
TI Ethnopharmacology of kratom and the Mitragyna alkaloids.
AU Jansen KL; Prast CJ
SO J Ethnopharmacol, (1988 May-Jun) 23 (1) 115-9.
Journal code: K8T. ISSN: 0378-8741.

✓ L27 ANSWER 46 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 18
AN 88:418344 BIOSIS
TI ISOLATED THROMBOCYTOPENIA IN PATIENTS INFECTED WITH HIV
TREATMENT WITH INTRAVENOUS GAMMA GLOBULIN.
AU BUSSEL J B; HAIMI J S
SO AM J HEMATOL 28 (2). 1988. 79-84. CODEN: AJHEDD ISSN: 0361-8609
AB Isolated thrombocytopenia occurs frequently in patients infected with HIV. Studies of mechanisms of thrombocytopenia and clinical response to therapy suggest that the thrombocytopenia is often antibody mediated (ITP). The best approach to treatment of these patients is uncertain in that the routine modalities (steroids, splenectomy, vinca alkaloids) that are used to increase the platelet count in patients with classic ITP are known to be immunosuppressive. We report here the results of intravenous gamma globulin (IVGG) treatment of 22 patients with HIV-related acute and chronic ITP who had severe thrombocytopenia and bleeding symptoms. Only one patient had an opportunistic infection at the time of treatment. Eight patients were homosexual, eight had hemophilia, three were i.v. drug abusers, two children had congenital acquisition of HIV, and one was the wife of an HIV + i.v. drug abuser. The average pretreatment platelet count was 22,000/.mu.l (hemophiliacs were treated at higher platelet counts than were the other patients), and the mean peak platelet count measured on days 5 to 8 was 182,000/.mu.l. Nineteen of 22 patients had peak platelet counts > 50,000/.mu.l following IVGG and 17/22 had peak counts > 100,000/.mu.l. After the initial infusions, all but three refractory patients could maintain adequate platelet counts with IVGG alone infused no more often than once every 2 weeks. The outcomes for the 22 patients after multiple maintenance IVGG infusion were remission, 5; stable without therapy, 1; maintenance, 13; and refractory, 3. The eight hemophiliacs with ITP responded better than did the eight homosexual ITP patients; their mean peak platelet count was 227,000/.mu.l versus 142,000/.mu.l in the homosexuals. In

summary, patients with HIV-related ITP without opportunistic infections responded well to IVGG, with peak platelet counts comparable to those of ITP patients not infected with HIV. IVGG may be a useful therapy of ITP in HIV + patients, since it appears to be less immunosuppressive than are conventional therapies, and none of the 22 HIV + patients developed an opportunistic infection while receiving IVGG alone.

✓ L27 ANSWER 47 OF 104 MEDLINE

AN 88075971 MEDLINE

TI Quantitative analysis of cell-kill effects of anticancer drugs: consideration of both in vitro and in vivo experimental systems.

AU Sugiyama Y; Kobayashi T; Inaba M

SO Gan To Kagaku Ryoho, (1987 Dec) 14 (12) 3183-98. Ref: 29

Journal code: 6T8. ISSN: 0385-0684.

AB After examining the in vitro cell-kill kinetics of various anticancer drugs by using cultured human cell lines, Shimoyama et al. classified the drugs into two groups according to the types of action: 1) type-I drugs (cytotoxic and concentration-dependent action) such as alkylating agents and anticancer antibiotics; 2) type-II drugs (cytostatic and time-dependent action) such as antimetabolites, Vinca alkaloids and L-asparaginase. In the present paper, we will present a rational basis for such a classification by using cell-kill pharmacodynamic models, and consider the optimal dosage regimen depending on the type of drugs by combining the cell-kill kinetic and pharmacokinetic models. In these models, classification of the drugs depends on whether the cell population is kinetically homogeneous or not. It is assumed that cell population is homogeneous for type-I drugs and there exist both drug sensitive and insensitive cell populations for type-II drugs. The concentration (or dose)-time-cell survival curves in both in vitro and in vivo, which are simulated based on the kinetic models, are consistent with the experimental data found in the literature. Further analysis on the optimal dose regimen according to these kinetic models clarified that the type-I drugs showed a similar cell-kill effect irrespective of the mode of administration as long as the area under the plasma unbound concentration curves (AUCp; free) is kept constant, while the type-II drugs are more effective by multiple dosing or infusion regimen than single administration of a large dose of drugs. In other words, the extents of AUCp, free and the residence time in the plasma (above certain concentrations of drugs) are determinants of the in vivo cell-kill effects of type-I drugs and type-II drugs, respectively. If the pharmacokinetics of newly developed anticancer drugs in human are predicted from the animal data according to the so-called "animal scale-up" technique and combined with the in vitro cell-kill kinetic data by the use of proposed kinetic models, one may obtain not only the optimal dosage regimen but also good screening systems for truly active drugs for the treatment of human cancer.

AN 87:486522 BIOSIS

TI DIHYDROERGOCRYPTINE IN MANAGEMENT OF MICROPROLACTINOMAS.

AU FAGLIA G; CONTI A; MURATORI M; TOGNI E; TRAVAGLINI P; ZANOTTI A; MAILLAND F

SO J CLIN ENDOCRINOL METAB 65 (4). 1987. 779-784. CODEN: JCEMAZ ISSN: 0021-972X

AB The effects of dihydroergocryptine (DHECP), a dihydrogenated ergot alkaloid with dopaminergic agonistic and .alpha.-adrenergic antagonistic properties, were studied in 22 women with PRL-secreting microprolactinomas and compared with those recorded in 36 previously studied patients treated with bromocriptine (BRC). After acute administration of 5 mg DHECP, orally, serum PRL decreased by 61 .+- 18% (.+-SD); only 1 patient was unresponsive. The nadir was reached at 300 min. Long term treatment with increasing DHECP doses caused a progressive PRL fall from 125 .+- 142 (.+-SD) to 81 .+- 159 .mu.g/L after 1 week of a 3 mg twice daily regimen, to 64 .+- 88 .mu.g/L after 1 week of 5mg twice daily, 46 .+- 57 .mu.g/L after 1 week of 10 mg twice daily, and 28 .+- 34 to 33 .+- 45 .mu.g/L throughout 9 months of treatment with 10 mg DHECP 3 times daily. Seventy-seven percent of patients had normal serum PRL levels during chronic treatment. All women, including those with supranormal serum PRL levels, resumed regular menses, and 16 had ovulatory cycles: 1 woman became pregnant. Galactorrhea disappeared in all. During treatment the PRL response to TRH, initially absent in all patients, became positive in 10. In 7 patients, after DHECP treatment for 9 months, high definition computed tomographic scan no longer showed the focal lesions initially seen. After drug withdrawal, serum PRL increased again in all except 1 patient. Two patients had regular menses for 6 months, and 3 still had no adenoma imaged by high definition computed tomography. In BRC-treated patients the serum PRL changes and clinical results were very similar to those in the DHECP-treated patients, except for the persistence of normal serum PRL levels in 4 patients after drug withdrawal. On the other hand, side-effects were negligible during DHECP treatment, but remarkable during BRC. Systolic and diastolic blood pressures decreased by only 5.4 and 3.0 mm Hg, respectively, after acute 5 mg DHECP administration, but decreased by 12.8 and 14 mm Hg after acute 2.5 mg BRC administration. Orthostatic hypotension and peripheral vasomotor phenomena occurred in the long term DHECP treated patients except one, but they occurred in 9 and 3 of those treated with BRC, respectively. Gastric discomfort or mild nausea occurred in 12 DHECP-treated patients, while mild or severe nausea or vomiting were observed in 18, 11, and 2 of those taking BRC, respectively. All patients tolerated 30 mg DHECP very well, while 2, 7, and 7 patients did not tolerate more than 2.5, 5.0, or 7.5 mg BRC, respectively. Six patients who did not tolerate BRC were treated with DHECP, and they had no significant side-effects. We conclude that DHECP is an effective and well tolerated PRL-lowering drug that may be useful for medical therapy of pathological hyperprolactinemia.

0 L27

AN 88143102 MEDLINE

TI A cyclic somatostatin analog that precipitates withdrawal in

AU morphine-dependent mice.

SO Shook JE; Pelton JT; Kazmierski W; Lemcke PK; Villar RG; Hruby VJ; Burks TF

AB NIDA Res Monogr, (1987) 76 295-301.

Journal code: NRM. ISSN: 1046-9516.

We evaluated the ability of the mu selective, peptidic, opioid antagonist CTP to precipitate withdrawal in morphine-dependent mice after intracerebroventricular (i.c.v.) and subcutaneous (s.c.) administration. The withdrawal syndrome evoked by i.c.v. CTP was different in some respects from that observed after i.c.v. naloxone. Naloxone, given i.c.v., produced shakes and tremors, defecation, diarrhea, wet dog shakes, jumping and weight loss. In contrast, the prominent signs following i.c.v. CTP were grooming, tremors and shakes, defecation, wet dog shakes and weight loss. CTP treated mice exhibited a greatly reduced incidence of jumping behaviors and diarrhea. While s.c. naloxone evoked similar effects to i.c.v. naloxone, CTP given s.c. stimulated defecation and modest weight loss only. The differences in the profile of withdrawal signs between naloxone and CTP may be related to their differences in receptor selectivity or possibly to their respective alkaloidal and peptidic natures. The relative lack of behavioral effects seen after s.c. CTP probably reflects the inability of CTP to pass through the blood brain barrier, and indicates that although the majority of withdrawal signs are mediated by centrally located opioid receptors, the gastrointestinal tract can be withdrawn independently of the central nervous system.

✓L27

AN 87181960 EMBASE

TI Chronic intake of a hydrogenated ergot alkaloid causing

AU peripheral vascular ischemia - A case report.

SO Hubens G.; Cham B.; Welch W.

VASC. SURG., (1987) 21/4 (295-298).

CODEN: VASUA

AB Ergotism is known to cause peripheral vascular ischemia. This case report describes the occurrence of peripheral gangrene in a thirty seven year old woman who had been taking a hydrogenated ergot alkaloid, ergoloid mesylates, 3 x 25 dr./24h, for nine years. Negative results from exhaustive clinical, laboratory and technical investigations and the disappearance of symptoms after withdrawal of the drug compel the conclusion that chronic intake of ergoloid mesylates led to the vascular problems presented by the patient. Six months after the second amputation of necrotic toes the patient was painfree and showed no signs of recurring ischemia. The amputation would have healed satisfactorily.

/ L27

AN 87271148 MEDLINE

TI [Pharmacological agents in controlling smoking].

- Farmakologicheskie sredstva v bor'be s kuren'em.
Metelitsa VI
SO Biull Vsesoiuznogo Kardiolog Nauchn Tsentra AMN SSSR, (1987) 10 (1)
109-12.
Journal code: AHS. ISSN: 0201-7369.
- ✓L27 ANSWER 52 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
AN 87049179 EMBASE
TI Intraarterial sodium nitroprusside infusion in the treatment
of severe ergotism.
AU Dierckx R.A.; Peters O.; Ebinger G.; et al.
SO CLIN. NEUROPHARMACOL., (1986) 9/6 (542-548).
CODEN: CLNEDEB
- ✓L27 ANSWER 53 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
AN 87002097 EMBASE
TI Adverse reactions and interactions with .beta.-adrenoceptor blocking
drugs.
AU Lewis R.V.; McDevitt D.G.
SO MED. TOXICOL., (1986) 1/5 (343-361).
CODEN: METOEV
- AB .beta.-Blocking drugs are widely used throughout the world and
serious adverse reactions are relatively uncommon. Most of those
which do occur are pharmacologically predictable and may
be avoided by ensuring that patients who are to be given
.beta.-blockers do not have a predisposition to the development of
bronchospasm, cardiac failure or peripheral ischaemia. In some
situations, the use of a .beta.1-selective blocking drug may reduce
the risk of a severe adverse reaction, but there is little evidence
that other ancillary properties such as partial agonist activity are
of relevance in this context. Long term experience with many of the
.beta.-blockers in current use suggests that unpredictable major
adverse reactions such as the practolol oculomucocutaneous syndrome
are unlikely to be repeated, although some of these drugs may be
associated with immunological disturbances and some have been
implicated in the development of retroperitoneal fibrosis.
.beta.-Blocking drugs appear to be associated with a number of
subjective side effects including muscle fatigue, peripheral
coldness and some neurological symptoms. These side effects are
highly subjective and are therefore difficult to quantify and it is
not known whether they are of major importance in terms of their
effect upon patients' overall wellbeing. It cannot be assumed that
simply because such side effects can be elicited that they do, in
fact, matter. However, because .beta.-blockers are often prescribed
for patients who have no symptoms and for whom the benefits of
therapy are generally small, such side effects would be of
considerable importance if they had an overall effect upon quality
of life. There are theoretical reasons to suppose that the incidence
and severity of such side effects may be related to the ancillary
properties of the individual drugs, but there is little evidence
that parameters such as .beta.1-selectivity, or partial agonist
activity are clinically important determinants of the severity of
these side effects. Lipophilicity, however, may be associated with

an increased incidence of neurological symptoms. .beta.-Blocking drugs may cause a variety of metabolic disturbances including an increase in serum VLDL-cholesterol concentrations. However, long term studies have not shown that such disturbances are associated with an increased risk of cardiovascular disease, indicating that such metabolic changes may not be of major importance in practice. .beta.-Blocking drugs may be involved in a number of interactions with other drugs, but few of these have been shown to be of clinical significance. The .beta.-blockers have a wide therapeutic ratio and differences in plasma concentrations may have little relevance in practice. However, .beta.-blockers may affect the disposition of other drugs and some of these may have narrow therapeutic ratios. Thus, in the case of warfarin, the concurrent administration of lipophilic .beta.-blockers may increase plasma warfarin concentrations and there is a possibility that this may be of some importance.

/L27

AN 87018928 EMBASE
TI Retroperitoneal fibrosis after long-term daily use of ergotamine.
AU Damstrup L.; Jensen T.T.
SO INT. UROL. NEPHROL., (1986) 18/3 (299-301).
CODEN: IURNAE

ANSWER 54 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

0 L27

AN 86:222181 BIOSIS
TI SURVIVAL RESPONSES TO NEW CYTOSTATIC HEXITOLS OF P-388 MOUSE AND K-562 HUMAN LEUKEMIA CELLS IN-VITRO.
AU PALYI I
SO CANCER TREAT REP 70 (2). 1986. 279-284. CODEN: CTRRDO ISSN: 0361-5960

ANSWER 55 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 20

AB The effects of four hexitol compounds [mitolactol, dianhydrogalactitol, 3,4-diacetyldianhydrogalactitol (DiacDAG), and 3,4-disuccinyldianhydrogalactitol]; two vinca alkaloids (vincristine and N-formylleurosine); doxorubicin; and methotrexate on colony formation of P388 and K562 cells were studied and compared. DisuDAG is a new derivative of hexitols with favorable therapeutic indices on rodent tumors. On the basis of IC50 values in molar concentrations, dianhydrogalactitol was five to six times more toxic than DiacDAG, and mitolactol was 36 (K562) or 80 (P388) times more toxic than DisuDAG. N-Formylleurosine was found to be 20 (P388) or 1000 (K562) times less toxic than vincristine. The large difference was due to the high resistance of K562 cells to N-formylleurosine. Both cell lines were very sensitive to doxorubicin: IC50 after 1 hour of exposure of P388 cells = 240 nM and after 1 hour of exposure of K562 cells = 275 nM. Continuous exposure to methotrexate resulted in 11 and 14.5 nM for P388 and K562 cells, respectively. We have not found direct correlation between the length of doubling times and drug sensitivity (doubling time of P388 = 13-14 hours and of K562 = 25 hours). The sensitivity of cell lines was rather tumor-specific and drug-dependent.

/L27

ANSWER 56 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

AN 86236917 EMBASE
 TI Ergotamine tartrate dependency: Features and possible mechanisms.
 AU Saper J.R.; Jones J.M.
 SO CLIN. NEUROPHARMACOL., (1986) 9/3 (244-256).
 CODEN: CLNEDEB
 AB Based on our clinical experience and the data reviewed and presented in this report, we propose that a state of physical dependency to ergotamine tartrate exists. This dependency state is characterized by the irresistible and dependable use of ergotamine tartrate and is contingent upon a self-sustaining, rhythmic headache/medication cycle that reflects the dependency. The headache and accompaniments (withdrawal headache?) represent the primary withdrawal symptoms. The presence of this state appears to render patients refractory to other forms of preventative therapy, which can be effective only when ergotamine is discontinued and the cycle broken. If the condition is left untreated, it is likely though by no means certain that the more traditional aspects of ergotism will evolve, although variable susceptibility and tolerance to ergotamine tartrate have been demonstrated. The mechanism of this disorder remains uncertain but might be related to the influence of ergotamine tartrate on the limbic-hypothalamic-pituitary-adrenal axis and other aminergic centers (locus ceruleus), areas considered by some as the central loci for the pathogenesis and associated symptoms of migraine.

✓127 ANSWER 57 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI..B.V.
 AN 86180603 EMBASE
 TI Recognition and treatment of arterial insufficiency from Cafergot.
 AU Wells K.E.; Steed D.L.; Zajko A.B.; Webster M.W.
 SO J. VASC. SURG., (1986) 4/1 (8-15).
 CODEN: JVSUES
 AB Cafergot is a combination of ergotamine tartrate and caffeine and may cause symptoms of peripheral vascular insufficiency. Iatrogenic ergotism should be suspected in any patient exhibiting ischemic symptoms while receiving this medication. Progression to fulminant necrosis and gangrene can occur. Two cases are presented and the management reviewed. This effect of ergotamine tartrate and caffeine may be an idiosyncratic hypersensitivity reaction with therapeutic doses or may result from excessive medication. Iatrogenic ergotism occurs most often in women in their mid-thirties with migraine syndrome. By .alpha.-adrenergic agonism, as well as by possible interactions with prostaglandins, calcium, and serotonin, ergotamine causes vasoconstriction of both arteries and veins. The angiographic pattern of spasm, collateral formation, and intravascular thrombi is typical. Treatment of ergotism depends on the severity of the symptoms and the possibility of gangrene. Discontinuation of ergotamine, cigarette smoking, and caffeine may be all that is necessary in most patients. Nitroprusside is the drug of choice in the treatment of acute vascular insufficiency from ergotism, but in a less urgent situation, prazosin has also been effective. Intra-arterial balloon dilatation has also been helpful. Other forms of therapy

have been supportive and the results inconsistent. Cafergot should be used with extreme caution in patients with renal or hepatic failure, peripheral vascular disease, or pregnancy. Relative contraindications include hypertension, ischemic heart disease, and Raynaud's phenomenon.

✓L27
AN 86011573 EMBASE
TI [The neuroleptic sleeping course in chronic headache].
AU DIE NEUROLEPTISCHE SCHLAFKUR BEIM CHRONIFIZIERTEN KOPFSCHMERZ.
SO Holzner F.; Barolin G.S.
THERAPIEWOCHE, (1985) 35/36 (4073-4079).
CODEN: THEWA6

AB A follow-up-study of 57 'chronic headache' patients undergoing medicamentous sleep with neuroleptics was done. We stress the predominance of patients with a typical combination of three factors: Headache plus depression plus drug abuse
Contrary to the general predominance of headache in women more than twice the number of patients were men. At first sight our therapy is almost completely successful (95%). At the end of an observation period over several years one-third of the patients still had positive therapeutic results. Within a population of analgesic-addicts this must be considered a fair result. This therapy can only be done in a hospital; the possible side effects and risks must be well understood and taken into consideration.

✓L27
AN 85103251 EMBASE
TI Drug-induced liver injury in liver biopsies of the years 1981 and 1983, their prevalence and type of presentation.
AU Koch H.K.; Gropp A.; Oehlert W.
SO PATH. RES. PRACT., (1985) 179/4-5 (469-477).
CODEN: PARPDS

AB Based on the histological picture of liver biopsies examined in the years 1981 and 1983, drug-induced liver injury has been suspected in 131 and 170 cases. In relation to the total number of the examined liver biopsies this accounted for 6 and 9.6%, respectively. In only 20 (i.e. 15%), respectively 17 (i.e. 10%) of the cases, a drug-induced injury could be clinically excluded. However, a drug-induced injury was doubtlessly secured in 21 (16%) and 28 (16.5%) of the cases. The histological phenotype seen in association with the incriminated drug is presented. In 90 (68.7%) and 125 (73.5%) of the cases it was neither possible to secure nor to exclude the drug as cause of this damage, either because in cases the clinical work-up was incomplete or because the drug-induced damage was clinically suspected, but not sufficiently documented by follow-up examinations after drug-withdrawal.

✓L27
AN 86003400 EMBASE
TI Drugs and fibrotic reactions - Part I.

ANSWER 58 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

ANSWER 59 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

ANSWER 60 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

- AU Castle W.M.
SO ADVERSE DRUG REACT. BULL., (1985) NO. 113 (420-423).
CODEN: ADRBBA
- J27 ANSWER 61 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
AN 85205995 EMBASE
TI Clinical pharmacokinetics of ergotamine in migraine and cluster headache.
AU Perrin V.L.
SO CLIN. PHARMACOKIN., (1985) 10/4 (334-352).
CODEN: CPKNDH
- AB Ergotamine has been in use for the treatment of migraine for a century and is still considered to be the most effective therapeutic agent for acute attacks. Only during the last few years have assays been developed, enabling its pharmacokinetics to be studied. Appropriate assays for determining ergotamine concentrations in plasma are radioimmunoassay and high-performance liquid chromatography. There is great interindividual variation in absorption of ergotamine in both patients and normal volunteers. Bioavailability is of the order of 5% or less by oral or rectal administration. After intramuscular or intravenous administration, plasma concentrations decay in a biexponential fashion. The elimination of half-life is 2 to 2.5 hours and clearance is about 0.68 L/h/kg. As yet, formal pharmacokinetics following oral dosing have not been determined. There is some evidence that ergotamine enters the cerebrospinal fluid. Metabolism occurs in the liver, and the primary route of excretion is biliary. Up to 90% of migraine patients experience complete or partial symptom relief after ergotamine, providing the drug is given as early in their attack as possible. Efficacy is greatest after parenteral administration, although adverse effects may make the rectal or inhaled routes preferable. There is some evidence to suggest that good responses are associated with plasma concentrations of 0.2 ng/ml or above within one hour of administration. The mode of action of ergotamine in migraine may be by means of selective arterial vasoconstriction on certain cranial vessels mediating pain transmission or circulatory regulation. Principal adverse effects of ergotamine include nausea, vomiting, weakness, muscle pains, paraesthesiae and coldness of the extremities. Ergotamine dependence is not uncommon, resulting in an exacerbation of the above symptoms. Dosage must therefore be limited to no more than 10 mg per week to minimise toxicity.
- J27 ANSWER 62 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
AN 85052857 EMBASE
TI Reversible ipecac myopathy.
AU Mateer J.E.; Farrell B.J.; Chou S.S.M.; Gutmann L.
SO ARCH. NEUROL., (1985) 42/2 (188-190).
CODEN: ARNEAS
- AB The abuse of ipecac syrup for three years resulted in painless, nonfatigable, chiefly proximal weakness in a 27-year-old woman. Electromyography (EMG) and a muscle biopsy revealed features of a

myopathy similar to those previously reported in experimental emetine myopathy. Clinical weakness and EMG abnormalities improved after discontinuation of ipecac administration. A direct toxic action of ipecac (acting through its active alkaloid, emetine hydrochloride) on muscle fibers seemed to be responsible for the weakness in this patient.

✓L27
AN 86022031 MEDLINE
TI Harmine-, LON-954- and 5-hydroxytryptophan-induced tremors in rats withdrawn from ethanol.
AU Gothoni P
SO Acta Pharmacol Toxicol (Copenh), (1985 Jul) 57 (1) 40-6.
AB Journal code: 1QG. ISSN: 0001-6683.

The tremors induced by harmine, LON-954 (N-carbamoyl-2-(2,6-dichlorophenyl)acetamide hydrochloride) and 5-hydroxytryptophan (5-HTP) were studied in control rats and in rats withdrawn for 16-48 hrs from 6 to 9 days' ethanol administration. The frequencies and the intensities of the tremors were determined electronically. In control rats the frequency spectra of the tremors induced by harmine (20 mg/kg) and LON-954 (10 mg/kg) showed a narrow peak frequency at about 10 Hz. Atropine (1.2 mg/kg) altered neither the frequency nor the intensity of these tremors. 5-HTP (50 mg/kg) when given 3.5 hrs after iproniazid (100 mg/kg) induced tremor with peak frequencies at 6-7 Hz and 12 Hz. In ethanol-withdrawn rats treated with harmine or LON-954 the frequency analysis of tremor revealed a narrow peak frequency at about 12 Hz, which was neither the characteristic frequency of ethanol withdrawal tremor (6 Hz) nor that of harmine or LON-954 (10 Hz). The intensity of both harmine- and LON-954-induced tremor was significantly increased in ethanol-withdrawn rats. The ethanol-withdrawn rats were markedly sensitized to the effect of iproniazid+ 5-HTP, shown by deaths. The peak frequencies of this tremor were the same as those in control rats. The results suggest that harmine-induced tremor involves a dopaminergic-5-HT'ergic imbalance and the tremor induced by LON-954 a dopaminergic-cholinergic imbalance in the brain. The tremor in ethanol-withdrawn rats seems to be mediated by alterations in the activity of the cerebral 5-HT'ergic system.

✓L27
AN 84179643 EMBASE
TI [Treatment of headache].
AU Isler H.
SO SCHWEIZ. MED. WOCHENSCHR., (1984) 114/35 (1174-1180).
AB CODEN: SMWOAS

ANSWER 64 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

84179643 EMBASE
[Treatment of headache].
DIE BEHANDLUNG DER KOPFSCHMERZEN.

Isler H.
SCHWEIZ. MED. WOCHENSCHR., (1984) 114/35 (1174-1180).
CODEN: SMWOAS

In symptomatic headache treatment is directed against the underlying disease. If this is impossible, its pathogenesis may still respond to treatment such as dexamethasone in inoperable brain tumor, simple psychotherapy in reactive emotional disorder due to intractability of the underlying disease, or migraine management where symptomatic headache is succeeded by migraine, as in posttraumatic headache. Primary headache-migraine,

cluster headache, and cephalaea vasomotoria ('tension headache') require positive identification of the syndrome but this does not lead directly to proper treatment; assessment of severity and, where feasible, of the psychological situation is needed. The means are available to influence some of the mechanisms apparent in primary headache both by non-drug and by drug treatment, but the choice must allow for the fact that these methods are not specific but only a little more effective than placebo. Drug abuse is the principal danger in headache problems. It can be treated by tracking down the offending drug under cover of interval medication or, failing this, by abrupt withdrawal in a neurology ward followed by a period of several weeks' exile from the usual daily demands. A short description of drugs used in primary headache is given.

✓ L27 ANSWER 65 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
 AN 85038579 EMBASE
 TI Clinical criteria for the selection of anxiolytics.
 AU Hoes M.J.A.J.M.
 SO TIJDSCHR. THER. GENEESM. ONDERZ., (1984) 9/9 (445-457).
 CODEN: TTTOE

L27 ANSWER 66 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
 AN 84182735 EMBASE
 TI Modern ergotism.
 AU Macquire A.M.; Cassidy J.T.
 SO AM. FAM. PHYS., (1984) 30/2 (179-183).
 CODEN: AFPYAE

AB A patient taking excessive amounts of an ergot alkaloid for the treatment of migraine headaches developed cool, painful, swollen lower extremities with intermittent claudication and sensory changes. Symptoms subsided and pulses returned within a day of cessation of therapy. 'St. Anthony's fire' may be due to stimulation of alpha-adrenergic receptors in the peripheral vasculature. Rebound headache after withdrawal of ergot alkaloids may lead to self-medication and overdose, with subsequent risk of ergotism.

✓ L27 ANSWER 67 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
 AN 84250015 EMBASE
 TI Reversible cerebral arteriopathy associated with the administration of ergot derivatives.
 AU Henry P.Y.; Larre P.; Aupy M.; et al.
 SO CEPHALALGIA, (1984) 4/3 (171-178).
 CODEN: CEPHDF

L27 ANSWER 68 OF 104 MEDLINE
 AN 84148457 MEDLINE
 TI [Treatment of nicotinic acid deficiency].
 AU Ob opyte lechenia nikotinizma.
 SO Marakulin VS; Komarov VM; Chuprin VV
 Voen Med Zh, (1984 Jan) (1) 55-8.
 Journal code: XGS. ISSN: 0026-9050.

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ANSWER 69 OF 104 MEDLINE
84011826 MEDLINE

Cytotoxicity and sister chromatid exchanges induced in vitro by six anticancer drugs developed in the People's Republic of China. Huang CC; Han CS; Yue XF; Shen CM; Wang SW; Wu FG; Xu B J Natl Cancer Inst, (1983 Oct) 71 (4) 841-7.

Journal code: J9J. ISSN: 0027-8874.

Growth inhibition in the Chinese hamster cell line V79 and in the human lymphoid cell line Raji and induction of sister chromatid exchange(s) (SCE) in V79 cells after treatment with six anticancer drugs [harringtonine (HRT), homoharringtonine (HHRT), camptothecin (CPT), hydroxycamptothecin (HCPT), lycobetaine (LBT), and oxalysine (OXL)] developed in the People's Republic of China were studied. OXL is a new antibiotic; all other drugs are plant extracts. All drugs caused a dose-dependent

growth inhibition in both cell types, as evidenced by decreases in plating efficiencies of V79 cells and in viable cell counts of Raji. However, the degree of inhibition differed widely among the drugs. HRT, HHRT, CPT, and HCPT were the most potent growth inhibitors, LBT was next, and OXL was the least effective inhibitor. SCE analyses were made in V79 cells treated with a drug in the presence or absence of the metabolic activation system S9 mixture (S9 mix), except for the HRT assay in which the S9 mix was not used. CPT, HCPT, and LBT induced a dose-dependent increase in SCE frequencies, while HRT, HHRT, and OXL caused no SCE induction at any dose level used. CPT was the most powerful SCE inducer. HCPT induced SCE but at a much reduced rate when compared to that of CPT. LBT was a weak SCE inducer; SCE induction was seen only in cultures treated with 40 micrograms or more LBT/ml. Addition of the S9 mix did not alter SCE frequencies, indicating that the drugs were direct-acting agents. HRT and HHRT were highly toxic, but they induced no increases in SCE frequency, indicating that cytotoxicity of a compound does not necessarily correlate with SCE induction.

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ANSWER 70 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
83167556 EMBASE

Successful treatment of opiate withdrawal using lysine acetylsalicylate.

Vescovi P.P.; Pezzarossa A.; Caccavari R.; Butturini U. CURR. THER. RES., CLIN. EXP., (1983) 33/5 (733-739).
CODEN: CTCEA

Lysine acetylsalicylate (LAS) was administered to 15 inpatient heroin addicts under methadone maintenance therapy after abrupt discontinuation of the drug, to determine possible usefulness of LAS in preventing the withdrawal syndrome in opiate alkaloid addicts. Lysine acetylsalicylate at a total daily dosage of 50 mg/kg/i.v. for 4 days, followed by a 25 mg/kg/day administration for 3 days and finally administered for a week at 1,800 mg/day orally was effective in preventing signs and symptoms of opiate withdrawal. Withdrawal effects were totally absent during the first 24 hours of treatment in all patients. Between

the 24th and 48th hour of the treatment, 5 out of 15 patients complained of insomnia and opiate craving. The degree of the symptoms did not require stopping or modifying the treatment and none of the patients chose to return to methadone after the treatment had started. Thus the hydrosoluble derivative of acetylsalicylic acid - lysine acetylsalicylate - represents an alternative, safe and effective means in the treatment procedures for opiate detoxification.

✓L27
AN 84039427
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ANSWER 71 OF 104 MEDLINE
84039427 MEDLINE

DUPLICATE 21

Energy-dependent reduced drug binding as a mechanism of Vinca alkaloid resistance in human leukemic lymphoblasts.

Beck WT; Cirtain MC; Lefko JL

Mol Pharmacol, (1983 Nov) 24 (3) 485-92.
Journal code: NGR. ISSN: 0026-895X.

We studied the accumulation of [^3H]vinblastine (VLB) by lines of CCRF-CEM cultured human leukemic lymphoblasts that were either sensitive or resistant to the drug. Neither cell line metabolized VLB, nor selectively retained any radioactive impurities. There was an apparent "instantaneous" accumulation of VLB by cells of both lines, resulting in cell to medium ratios greater than 1.0 within 1 sec after drug addition. Experiments between 0 and 60 sec revealed that the presumed unidirectional initial rate of VLB accumulation by resistant cells, termed CEM/VLB100, was about one-half that of sensitive CEM cells. In experiments carried out over 60 min, the VLB-resistant cells accumulated considerably less [^3H]VLB than did the sensitive cells. Drug accumulation by both cell lines was temperature-sensitive, since incubation of cells at 4 degrees resulted in only minimal uptake beyond that observed at zero time. CEM/VLB100 cells retained less drug than did CEM cells, apparently because of a larger fraction of readily releasable VLB compared with CEM cells. The accumulation of VLB by either cell line was related in part to cellular levels of ATP. Although depletion of ATP was associated with decreased accumulation of VLB by CEM cells, it was related to enhanced drug accumulation by CEM/VLB100 cells. Restoration of ATP levels to near control values by addition of glucose also had opposite effects on the two cell lines, causing further accumulation of VLB by the sensitive line but leading to apparent drug efflux from the resistant line. Potentially competing substrates (VM-26, colchicine, daunorubicin, and doxorubicin) failed to block this glucose-mediated release of VLB from the CEM/VLB100 cells. In experiments with energy-depleted CEM/VLB100 cells preloaded with VLB and then incubated in drug-free medium, initial drug loss was shown to be independent of cellular metabolism, being roughly the same for both metabolically intact and metabolically depleted cells. Glucose (energy) was required only for subsequent release of what appeared to be a more tightly bound cell-associated fraction of VLB. Results of zero-time binding studies tended to confirm that VLB binding by resistant cells has two components, one requiring and the other not requiring

metabolic energy. Differences in the proportions of the two components between the sensitive and resistant cells suggest a mechanism for resistance to VLB and similar compounds.

✓L27 ANSWER 72 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

AN 83129017 EMBASE

TI The 'Alice in Wonderland' experience. Ergot alkaloid therapy for prolactin-secreting pituitary tumors.

AU Williams R.C. Jr.; Sherman C.; Buckman M.T.

SO WEST. J. MED., (1983) 138/3 (391-397).

CODEN: WJMDA2

AB The development of new ergot alkaloid derivatives with dopamine-agonist activity has had a major impact on the treatment of human prolactin-secreting pituitary adenoma. Akin to Alice's experiences in Alice in Wonderland, the tumors have been shown to contract and expand on administration or withdrawal of dopamine-agonist drugs. Although medical therapy does not appear to be curative for macroprolactinoma at this time, it does offer an alternative of adjunct to other modalities of therapy. Research regarding optimal dosage, timing and duration of therapy - as well as possible development of newer and better drugs - may yield yet more optimistic results in the future. For the time being, dopamine-agonist drugs offer a potent palliative alternative adjunct to surgical and radiation therapy. A few studies have suggested that hyperprolactinemia may be associated with significant psychologic distress. Attention to assessment of the psychologic state in hyperprolactinemic persons may uncover significant symptomatology that may benefit from dopamine-agonist treatment independent of other indications for such therapy.

✓L27 ANSWER 73 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

AN 84040711 EMBASE

TI Effects and risks of psychotropic and analgesic combinations.

AU Worz R.

SO AM. J. MED., (1983) 75/5A (139-140).

CODEN: AJMEAZ

AB Psychotropic substances combined with simple analgesics are a common pharmacologic denominator in the dependency complex. More than 95 percent of patients studied took preparations containing barbiturates; the remaining few subjects used analgesics combined with caffeine. Dependence on compound analgesic preparations usually develops in patients with headaches - migraine, tension headaches, and other complex forms - since ergotamine-containing preparations are generally effective only at the onset of an attack, and prophylactic administration is, therefore, common. Once dependence has developed, reduction or discontinuation of the medication is typically followed after one or two days by an increase in the intensity of the pain. This may cause the patient to revert to these preparations in an attempt to reduce pain and may lead to an unfortunate vicious cycle. Therefore, cessation of psychotropic analgesic combinations is essential in the

treatment of chronic pain.

✓L27 ANSWER 74 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
 AN 85194396 EMBASE
 TI [History of use of psychotropic drugs in central Africa].
 DE L'ANCIENNETE DE L'USAGE DES PSYCHOTROPES EN AFRIQUE CENTRALE.
 AU Janzen J.M.
 SO PSYCHOTROPES, (1983) 1/2 (105-107).
 CODEN: PSCTEO

L27 ANSWER 75 OF 104 MEDLINE
 AN 83223142 MEDLINE

TI [Clinical and electrophysiologic changes produced by (--) eburnamonine in acute and post-acute stages of head injuries].
 Modificazioni cliniche ed elettrofisiologiche indotte dalla (--) eburnamonina nei traumatizzati cranici in fase acuta e post-acuta.
 AU Facciolla D; Ruocco A; Rossi A; Serra C; Bufalino L; Cavrini P
 SO Riv Neurol, (1983 Jan-Feb) 53 (1) 15-33.
 Journal code: TOX. ISSN: 0035-6344.

AB Two groups of patients suffering from cranial trauma have been submitted to a double-blind acute (1-2 per phlebo ampules/die for 7-10 days) and chronic (1 i.m. ampule for 30 days) at random treatment, respectively with (--) Eburnamonine and Papaverine. The evaluation of the clinical symptoms (state of consciousness, neurologic and post-traumatic symptoms) and of some electrophysiological responses (REG, visual and somato-sensorial evoked potentials) were investigated in basal conditions, during the acute stage, at the end of the chronic treatment and 30 days after the drugs withdrawal. The results showed (--) Eburnamonine to induce a superior improvement than Papaverine of some clinical symptoms (motor disorders, retrograde amnesia, vertigo) and of cortical bioelectrical activity, as rheoencephalographic data and reduction in early latencies of evoked response to somato-sensorial stimulation (SEP) revealed. Local and systemic tolerability was good with both drugs; a slight hypotensive action, more marked with Papaverine, was noted at the end of the treatment.

✓L27 ANSWER 76 OF 104 MEDLINE
 AN 83024776 MEDLINE

TI In vivo resistance towards anthracyclines, etoposide, and cis-diaminedichloroplatinum(II).
 AU Seeber S; Osieka R; Schmidt CG; Achterrath W; Crooke ST
 SO Cancer Res, (1982 Nov) 42 (11) 4719-25.
 Journal code: CNF. ISSN: 0008-5472.
 AB From a single wild-type strain of Ehrlich ascites tumor, sublines resistant to daunorubicin, etoposide, and cis-diaminedichloroplatinum(II) have been developed in vivo. Different levels of resistance were achieved after 4 to 8 months for anthracyclines (greater than 32-fold), cis-diaminedichloroplatinum(II) (4-fold), and etoposide (greater than 6-fold). Anthracycline resistance was associated with decreased nuclear steady-state concentration of anthracyclines, increased

content of high-molecular-weight membrane glycoproteins, and glucose-dependent drug extrusion after metabolic blockade with sodium azide. A similar "pump" system which was apparently not drug specific was also documented in etoposide resistance. Resistance towards cis-diamminedichloroplatinum(II) was accompanied by decreased cis-diamminedichloroplatinum(II)-induced DNA damage in vitro when proteinase K-resistant interstrand cross-links were measured by alkaline elution. Parallel in vivo studies revealed cross-resistance of various degrees among a number of anthracycline analogs, complete cross-resistance among daunorubicin, doxorubicin, and 4'-(9-acridinylamino)methanesulfon-M-anisidine (amsacrine), and partial cross-resistance between daunorubicin and etoposide. However, cis-diamminedichloroplatinum(II) was curative in anthracycline- and etoposide-resistant cells, as daunorubicin and etoposide were curative in acquired resistance towards cis-diamminedichloroplatinum(II). cis-Diamminedichloroplatinum(II) resistance was also overcome by the derivative 1,2-diaminocyclohexylplatinum malonate. The Vinca alkaloid vindesine, although only marginally active in the control tumor, was highly active in cells selected for cis-diamminedichloroplatinum(II) resistance. These in vivo patterns of cross-resistance and collateral sensitivity may be related to observations in clinical chemotherapy.

127 ANSWER 77 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

AN 83066097 EMBASE

TI Gangrene of the small bowel: A complication of methysergide therapy.

AU Menzies K.E.; Isbister W.H.

SO AUST. N. Z. J. SURG., (1982) 52/5 (510-511).

CODEN: ANZJA7

AB A 49 year old woman with mesenteric vascular fibrosis resulting in infarction of the small bowel after taking methysergide for migraine prophylaxis is presented. Only one other report of this complication of methysergide therapy has been found in the literature although two patients with mesenteric angina have been documented. It appears that timely withdrawal of the drug results in the reversal of the fibrotic process.

127 ANSWER 78 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

AN 83109062 EMBASE

TI Ergotamine abuse: Results of ergotamine discontinuation, with special reference to the plasma concentrations.

AU Ala Hurula V.; Myllyla V.; Hokkanen E.

SO CEPHALALGIA, (1982) 2/4 (189-195).

CODEN: CEPHDF

AB Twenty-three patients suffering from continuous headache linked with habitual daily use of ergotamine tartarate were studied. Their headaches were classified clinically, and possible side effects of ergotamine medication, plasma levels of ergotamine, and occurrence of withdrawal symptoms after discontinuation of drug abuse were recorded. Seventeen of the patients were

clinically diagnosed as suffering from 'ergotamine headache', and seven of them complained of coldness in the extremities. Plasma ergotamine levels were measured by using a radioimmunoassay. In almost half of the patients the 1 h plasma levels after the daily dose were below the detection limit of the procedure (0.12 ng/ml). The duration and severity of the withdrawal symptoms did not correlate with the doses and plasma levels of ergotamine. In only 4 of 21 patients who were followed up for 3 to 6 months did headache symptoms not improve after ergotamine withdrawal. The results indicate that even small (0.5-1.0 mg/day) doses of ergotamine tartrate taken regularly may cause continuous headache symptoms and withdrawal symptoms after discontinuation.

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ANSWER 79 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
82144824 EMBASE
Nitroglycerin for ergotism. Experimental studies in vitro and in migraine patients and treatment of an overt case.
Tfelt-Hansen P.; Ostergaard J.R.; Gothgen I.; et al.
EUR. J. CLIN. PHARMACOL., (1982) 22/2 (105-109).
CODEN: EJCPAS

Ergotamine was used to induce arterial contraction in vitro (measurement of isometric tension in segments from 3 human temporal arteries) and in vivo (peripheral systolic blood pressure measured by strain gauge plethysmography in 5 migraine patients). In both these models of ergotism, the directly acting vasodilator nitroglycerine (NTG) effectively relieved the ergotamine-induced arterial contractions. A case of ergotism treated successfully with NTG infusion is reported. The diagnosis was based on history and measurement of peripheral systolic blood pressure by strain gauge plethysmography. The latter technique was also used to monitor the response to treatment for 20 h. Blood levels of ergotamine during ergotism were in the therapeutic range. Possible explanations for this finding are discussed.

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ANSWER 80 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS
81:247624 BIOSIS
EFFECTS OF ACRONYCINE AND CYTOCHALASIN B ON THE DIVISION OF RAT LEUKEMIA CELLS.
LOW R S; AUERSPERG N
EXP CELL RES 131 (1). 1981. 15-24. CODEN: ECREAL ISSN: 0014-4827
Acronycine (AN) is a lipophilic antineoplastic alkaloid which, like cytochalasin B (CB), inhibits nucleoside transport and causes binucleation through interference with cell cleavage. Unlike (CB, AN causes swelling of membranous organelles and does not inhibit microfilament-mediated epithelial cell contractions. The effects of AN (6-12 .mu.g/ml) and CB (1.5-4 .mu.g/ml) on cell division were compared by direct observation and time-lapse cinemicrography in cultured IRC 741 rat leukemia cells. Both drugs caused dose-dependent binucleation and inhibition of the normal increase in cell numbers with the effects of 12 .mu.g/ml AN approximating those of 4 .mu.g/ml CB. In cells entering division after exposure to the drugs for up to 24 h, furrowing was completely inhibited in a dose-dependent proportion of cells by CB but not by

AN. In cells where furrowing occurred, the intervals from the onset of anaphase to furrow initiation were shortened significantly by 1.5-3 .mu.g/ml CB, but not by 4 .mu.g/ml CB; they were also shortened after 4-6 h of 12 .mu.g/ml AN, but were prolonged up to 60% by 7-24 h of 12 .mu.g/ml AN. Intervals from furrow initiation to daughter cell separation were prolonged up to 50% by AN and 140% by CB. The intervals from onset of anaphase to nuclear membrane reconstitution were not affected by AN for up to 18 h and lengthened thereafter; they were shortened by CB after 3-19 h, depending on the dose. In AN-treated cells, single furrows formed and cleavage was accompanied by twisting and exaggerated elongation along the long axis of the dividing cells, while CB-treated cleaving cells were characterized by surface blebbing and the formation of several consecutive incomplete furrows. Most CB effects occurred rapidly, while AN effects were delayed. Apparently, the modes of action of CB and AN differ. AN apparently interferes primarily with the structure, function and/or turnover of cell membrane components.

✓ L27 ANSWER 81 OF 104 MEDLINE

AN 81063075 MEDLINE

TI Drug dependent red cell antibodies and intravascular haemolysis occurring in patients treated with 9 hydroxy-methyl-ellipticinum.

AU Criel AM; Hidayat M; Clarysse A; Verwilghen RL

SO Br J Haematol, (1980 Dec) 46 (4) 549-56.

Journal code: AXC. ISSN: 0007-1048.

AB Eleven patients were treated weekly with a new cytostatic drug, 9-hydroxy-methyl-ellipticinum (9 HME). Eight were treated for longer than 4 weeks and three of these developed a drug dependent antibody reacting with normal red cells. In two of these patients acute intravascular haemolysis occurred, one with oliguric renal failure; in the third patient the drug was stopped as soon as the antibody was detected. In all three patients the antibody developed after 4 weeks of treatment.

. It was IgM, agglutinated normal red cells and bound complement only in the presence of the drug. No antibodies could be detected in the patient's serum reacting with normal platelets in the presence of the drug. The incidence of haemolysis with this drug is much higher than seen with other drugs causing immune-complex haemolysis. Studies done with closely related substances suggest that the antigenic site of the drug is related to the group attached to carbon atom 9.

✓ L27 ANSWER 82 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

AN 80124334 EMBASE

TI Effect of methadone dosage on clonidine detoxification efficacy.

AU Gold M.S.; Pottash A.L.C.; Sweeney D.R.; Kleber H.D.

SO AM. J. PSYCHIATRY, (1980) 137/3 (375-376).

CODEN: AJPSAO

AB The use of methadone as a withdrawal agent has alleviated some of the problems associated with detoxification from opiate alkaloids. However, methadone presents its own abuse and dependence problems. Approximately 100,000 patients are receiving

methadone maintenance, and an unknown number are purchasing illicit methadone. The outlook for such people when they try to become opiate-free is quite poor. Studies to date indicate that the majority of patients who are in the process of slow methadone detoxification do not succeed in becoming methadone-free, and the majority of those who do reach a methadone-free state do not remain abstinent. We have recently reported that a single dose of clonidine given in a placebo-controlled study caused a rapid and significant decrease in opiate withdrawal signs and symptoms in heroin addicts and inpatients addicted to methadone at an average dose of 35 mg. We suggested on the basis of an open pilot outpatient study that clonidine might be an effective method for the rapid detoxification of methadone maintenance patients. The authors present evidence which suggests that clonidine is equally effective in suppressing the symptoms and signs of methadone withdrawal from low (15 mg), medium (50 mg), and high (75 mg) doses of methadone. We have found that 100% of patients have become opiate and clonidine-free in 14 days or less.

✓L27

AN 80:282003 BIOSIS COPYRIGHT 1994 BIOSIS

TI USE AND ABUSE OF ALCOHOL AND DRUGS A

AU CLINICAL STUDY OF CERTAIN ASPECTS OF THEIR INTERRELATIONSHIP.
ALMEIDA-V M

SO BOL OF SANIT PANAM 88 (1). 1980. 45-54. CODEN: BOSPA8 ISSN: 0030-0632

AB Alcoholic patients may be potential addicts to other toxic substances that induce dependency.

Alcoholics [210], most of whom were being treated by private physicians, were studied. Of the group 2/3 were ambulatory and were predominantly males, most of them aged from 30-45 yr. A study of their cases based on the type of drug involved showed that abuse was limited in 16 cases to such specific hypnotic drugs as phenobarbital and methaqualone, while in others there was a concomitant use of alcohol and sedatives. Patients [6] have made combined or successive use of such psychostimulants as amphetamines, 2 were additionally addicted to chewing coca leaves, and another 3 regularly associated the ingestion of ethanol with nasal aspiration of crystallized cocaine. As for tobacco, 90% of the members of the group smoked from 10-20 cigarettes a day. An additional study was made of the use and abuse of alcohol among 26 drug addicts, most of them between 18-21 yr of age. Members of this group [14] were addicted to cannabis, 6 to cocaine paste, 2 to methaqualone and 1 to socegon. Also, 21 had experimented with or made occasional use of such other substances as LSD, industrial solvents or glues, ethyl chloride, etc. As for alcohol, 16 of these patients customarily drank to the point of intoxication at least once a week; those who drank most frequently were the cannabis addicts, while the other 10 were moderate drinkers. With respect to drug dependence in Peru, it was noted that the 2 most important drug problems are alcohol and coca, which are the most widely consumed and present the gravest medical and social implications. As of 1970, annual consumption of pure

alcohol in that country was more than 55 million liters and the number of dependents was estimated at 303,965. Later studies showed that consumption levels and the number of alcoholics continue to rise. Taking the 1972 census figures as a basis, it was estimated that some 150,000 male students between the ages of 15-19 in urban zones had, on at least 1 occasion, drunk to the point of intoxication. Where drugs used by the youngest sectors of the Lima population were concerned an important point was the conspicuously spreading use of cocaine paste, with an average 40% alkaloid content, that had occurred since 1974. The mastication of coca leaves constituted the most usual form of drug dependence among a vast sector of the rural population.

✓L27

ANSWER 84 OF 104 MEDLINE

AN 80091713 MEDLINE

TI Effect of ergot alkaloids on serum prolactin in non-psychotic organic brain syndrome of the elderly.

AU Gross RJ; Eisdorfer CE; Schiller HS; Cox G

SO Exp Aging Res, (1979 Aug) 5 (4) 293-302.

Journal code: EN0. ISSN: 0361-073X.

AB A compound of ergot alkaloids (Hydergine-Sandoz)

or placebo was given to sixty elderly nursing home patients with non-psychotic organic brain syndrome. Subsequent to 12 weeks of treatment, the mean serum prolactin of the drug was significantly lower than that of the placebo group. No correlation was found between changes in prolactin and changes in behavior using Sandoz Assessment of Clinical Status Rating Form-Geriatric [SCAG]. It may be that a higher dose of Hydergine with an accompanying greater drop in prolactin would be required to observe this effect.

✓L27

ANSWER 85 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

AN 80035017 EMBASE

TI Azidomorphines: A new family of potent analgesics with low dependence capacity.

AU Knoll J.

SO PROG. NEURO-PSYCHOPHARMACOL., (1979) 3/1-3 (95-108).

CODEN: PRNPDP

AB Structure-activity relationship studies with new semi-synthetic isomorphine derivatives revealed that substitution of an azido group in position 6 (azidomorphines) greatly increases the analgesic potency whereas tolerance and dependence liability tend to decrease. Azidomorphine (6-deoxy-6-azidodihydroisomorphine) and 14-hydroxyazidomorphine (6-deoxy-6-azidodihydro-14-

hydroxyisomorphine) being in animal tests 40-300 times more potent than morphine, are the most effective analgesics among the semi-synthetic morphine alkaloids. As demonstrated on mice, rats and rhesus monkeys, a remarkable dissociation between the analgesic potency and physical dependence capacity was the result of the introduction of the 6-azido group into dihydroisomorphine. A dichotomy between analgesic effect and tolerance and addiction liability was demonstrated with azidomorphine also in man and the new substance proved to exert significantly less untoward effects than either morphine or pentazocine. Rymazolum (Probon) a new

non-narcotic analgesic which strongly potentiates the analgesic and antagonizes the respiratory depressant effect of morphine alkaloids in animals proved to hinder the development of tolerance to morphine in animals and man. The azidomorphine-rymazolium association was found to be less respiratory depressant than azidomorphine administered alone. In patients with chronic intractable pain, an association of azidomorphine (0.5 mg) and rymazolium (150 mg) achieved total pain relief without noticeable euphoria and none of the 12 patients showed, according to the Himmelsbach scoring system, acute abstinence syndromes after nalorphine administration.

✓ L27

ANSWER 86 OF 104 MEDLINE

AN 79213194 MEDLINE

TI Buprenorphine: a review of its pharmacological properties and therapeutic efficacy.

AU Heel RC; Brogden RN; Speight TM; Avery GS

SO Drugs, (1979 Feb) 17 (2) 81-110. Ref: 130

Journal code: EC2. ISSN: 0012-6667.

AB

Buprenorphine, a derivative of the morphine alkaloid thebaine, is a strong analgesic with marked narcotic antagonist activity. In studies in relatively small groups of postoperative patients with moderate to severe pain, one or a few doses of buprenorphine parenterally (by intramuscular or slow intravenous injection) or sublingually were at least as effective as standard doses of other strong analgesics such as morphine, pethidine or pentazocine, and buprenorphine was longer acting than these agents. Only a small number of patients with chronic pain have received repeated doses, but in such patients there was no need for increased doses during several weeks to months of treatment. Buprenorphine appears to produce side effects which are similar to those seen with other morphine-like compounds, including respiratory depression. There is apparently no completely reliable specific antagonist for buprenorphine's respiratory depressant effect, since even very high doses of the antagonist drug naloxone may produce only a partial reversal. The respiratory stimulant drug doxapram has overcome respiratory depression in volunteers and in a few patients in a clinical setting, but such studies have not been done in an overdose situation. Animal studies and a direct addition study in a few volunteers suggest that the dependence liability of buprenorphine may be lower than that of other older morphine-like drugs. However, a slowly emerging abstinence syndrome did occur on withdrawal after very high doses administered for 1 to 2 months. A definitive statement on the drug's dependence liability and abuse potential cannot be made until it has had much wider use for a longer period of time.

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ANSWER 87 OF 104 MEDLINE

AN 79129461 MEDLINE

TI [Psychiatric intensive therapy after acute alkaloid withdrawal syndrome].

Zur psychiatrischen Intensivtherapie des akuten

Alkaloidentzugssyndroms.

AU Konig P

SO Infusionsther Klin Ernahr, (1979) 6 (1) 56-9.

Journal code: GOI. ISSN: 0378-0791.

AB Two groups of patients (nine patients each) were treated for acute alkaloid-withdrawal-syndromes. One group was given peroral neuroleptic medication, the other was treated by neuroleptic cocktail administered via vena subclavia catheter. By statistic comparison of the two methods the superiority of the latter could be shown in that duration of withdrawal, the syndrome itself and hallucinatory transitional psychoses could be drastically reduced. A suitable prescription and dosages of the neuroleptic cocktail are presented. The results are compared to the ones in current literature.

✓L27

ANSWER 88 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.

AN 79005459 EMBASE

TI Phencyclidine identification by thin-layer chromatography. A rapid screening procedure for emergency toxicology.

AU Finkle H.I.

SO AM. J. CLIN. PATHOL., (1978) 70/2 (287-290).

CODEN: AJCPAI

AB The clinical manifestations of phencyclidine abuse may include bizarre neuropsychiatric symptoms, which may mimic the untoward reactions of a variety of illicit drugs. Specific diagnosis and therapy depend, primarily, upon consideration of this drug followed by its prompt and accurate identification. A rapid modified thin-layer chromatographic technic for the detection and differentiation of phencyclidine from other alkaloids and neutral drugs with similar R(f) values in this system is presented.

✓L27

ANSWER 89 OF 104 MEDLINE

AN 78184933 MEDLINE

TI Putative role of isoquinoline alkaloids in alcoholism: a link to opiates.

AU Blum K; Hamilton MG; Hirst M; Wallace JE

SO Alcohol Clin Exp Res, (1978 Apr) 2 (2) 113-20. Ref: 41

Journal code: 35X. ISSN: 0145-6008.

AB Although the isoquinoline hypothesis has stimulated and even tantalized the scientific inquiry of a small number of investigators, it has been an area of widespread controversy. For the most part, until recently, alcohol researchers would ascribe very little importance to the role played by isoquinolines in alcohol actions or in the disease state known as alcoholism. To most, there was adequate evidence that these condensation amines had potent pharmacologic properties but little was known about their biochemical and behavioral interaction with ethanol or opiates. As pointed out here, there is an increasing amount of evidence that indicates the putative role of isoquinolines as regulators of alcohol dependence. There is even evidence that suggests a possible "link" to opiates. If this turns out to be the case, then it is rational to consider the possibility that when one imbibes alcohol a central opiate-like substance is, in

essence, produced. It would appear that the sum total of evidence to date supports the notion that there are common territories between the two highly addictive classes of drugs--alcohol and opiates. Although still not definite, future studies may well confirm the intermediacy of the TIQ compounds.

✓L27

ANSWER 90 OF 104 MEDLINE

AN 77182839 MEDLINE

TI Recurrent laryngeal nerve paralysis in patients receiving vincristine and vinblastine.

AU Whittaker JA; Griffith IP

SO Br Med J, (1977 May 14) 1 (6071) 1251-2.

Journal code: B4W. ISSN: 0007-1447.

AB Three patients receiving vincristine or vinblastine developed recurrent laryngeal nerve paralysis, which resolved when the drug was withdrawn. The presence of mediastinal lymphadenopathy in patients with lymphoma may obscure the correct

diagnosis, with the danger that the condition will produce respiratory distress if vinca alkaloid treatment is continued.

✓L27

ANSWER 91 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS DUPLICATE 22

AN 78:186323 BIOSIS

TI PEYOTE A POTENTIAL ETHNO PHARMACOLOGIC AGENT FOR ALCOHOLISM AND OTHER DRUG DEPENDENCIES POSSIBLE BIOCHEMICAL RATIONALE.

AU BLUM K; FUTTERMAN S L; PASCAROSA P

SO CLIN TOXICOL 11 (4). 1977 (RECD 1978) 459-472. CODEN: CTOXAO ISSN: 0009-9309

AB Folk psychiatry among North American Indians was examined from an ethnopharmacologic viewpoint. Alcohol and opiate abuse among Indians and non-Indians was presented in case histories proving to be asymptomatic under Indian guidance and through participation in the peyote ritual. The biochemical alkaloids common in the peyote cactus, rather than just the psychoactive substances (mescaline), are pharmacologically similar to the neuroamine-derived alkaloids found in the brain during alcohol intoxication. Possible common features of alcohol and opiate dependence were examined, a common mode of treatment may reside in plants rich in isoquinoline alkaloids.

✓L27

ANSWER 92 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS

AN 78:204906 BIOSIS

TI ADRENERGIC NERVE DEGENERATION INDUCED BY CONDENSATION PRODUCTS OF ADRENALINE AND ACETALDEHYDE.

AU AZEVEDO I; OSSWALD W

SO NAUNYN-SCHMIEDEBERG'S ARCH PHARMACOL 300 (2). 1977 139-144. CODEN: NSAPCC ISSN: 0028-1298

AB Adult and newborn rats were treated with MA 3 or MA 4

(tetrahydroisoquinoline alkaloids resulting from the condensation of adrenaline [epinephrine] with acetaldehyde) to investigate the action of these alkaloids on the adrenergic

innervation. The irides, right heart auricles and superior cervical ganglia of control and treated rats were processed for microscopy and spectrofluorimetric determination of noradrenaline (NA) [norepinephrine]. Marked ultrastructural alterations of the adrenergic nerve terminals were observed in the irides and auricles of the treated adult and newborn rats. The superior cervical ganglia of the adult rats exhibited only minor ultrastructural alterations while those of the newborn animals presented anomalies even at the light microscopy level. Absence of significant alterations of the NA content in treated adult rats is attributed to the accumulation of fluorescing alkaloid derivatives. Apparently, MA 3 and MA 4 can induce selective degeneration of the adrenergic nerve terminals of the adult rats and of the whole adrenergic neuron of newborn rats. They were, in this respect, less potent than 6-OHDA [6-hydroxydopamine]. Since these alkaloids may be formed in vivo during ethanol intoxication, the results may contribute to the understanding of some of the phenomena related to ethanol intoxication and/or the alcohol withdrawal syndrome.

✓L27 ANSWER 93 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS

AN 78:136686 BIOSIS

TI PREFERENCE FOR ALCOHOL EVOKED BY TETRA HYDRO PAPAVEROLINE CHRONICALLY INFUSED IN THE CEREBRAL VENTRICLE OF THE RAT.

AU MELCHIOR C L; MYERS R D

SO PHARMACOL BIOCHEM BEHAV 7 (1). 1977 19-36. CODEN: PBBHÄU ISSN: 0091-3057

AB The voluntary preference for ethyl alcohol in Sprague-Dawley rats was determined over 12 days with H₂O as the alternative fluid. The alcohol solutions offered to the animals were increased systematically in concentrations from 3 to 30%, according to a 3-bottle, 2-choice technique. Tetrahydropapaveroline (THP), a tetrahydroisoquinoline derivative, was infused repeatedly into the lateral cerebral ventricle of each rat through a guide tube implanted chronically. The metabolite was dissolved in a CSF vehicle and infused in a volume of 1.0 .mu.l every 15 min or 4.0 .mu.l every 30 min around the clock, for the entire 12-day period of alcohol-water self-selection. Within 3-6 days of the start of infusion, extraordinary amounts of alcohol were consumed which ranged as high as 8-17 g/kg per day. Both the racemic mixture of THP and the S-(-)-THP isomer exerted this alcohol-inducing effect, when they were infused chronically in a range of doses from 100 pg/.mu.l to 1.0 .mu.g/ml. Control intraventricular infusions of CSF according to the same regimen had no effect on alcohol preference. The excessive intake of alcohol during the intraventricular infusions of THP persisted long after the cessation of the infusion regimen, i.e., during retests carried out at 1, 6 and 9 mo. intervals. When THP-treated rats were offered a simultaneous choice of a palatable solution of saccharin together with alcohol, they continued to drink large volumes of alcohol. The 24 h patterns of fluid intake, as registered continuously by a drinkometer, revealed that alcohol drinking was typically massed within 2-4 bouts during the night-time interval. During this period, the blood alcohol level reached

concentrations as high as 0.2%. Withdrawal-like symptoms including wet-dog shakes, elevated tail, whisker twitching and occasional convulsive episodes, were also observed in the THP-infused rats. An alkaloid metabolite, which may be formed in both the brain and periphery, is probably involved in the mechanism underlying the pathological and sustained drinking which is characteristic of the disease state of alcoholism.

✓ L27 ANSWER 94 OF 104 MEDLINE
AN 78077627 MEDLINE
TI Azidomorphines and homopyrimidazols: a new approach to the ideal analgetic.

AU Knoll J

SO Acta Physiologica Pharmacologica Bulg, (1977) 3 (2) 3-11.

Journal code: ISL. ISSN: 0323-9950.

AB Azidomorphines, new semi-synthetic isomorphine alkaloids and homopyrimidazols (1, 5-diazanaphthalenes), two new families of compounds favourably enlarging the scope of analgetics, were developed. Azidomorphine, a 40--50 times more potent analgetic in man than morphine, showed a remarkably great dissociation between analgetic potency and dependence capacity and proved to exert significantly less unfavourable effects than either morphine or pentazocine. Probon (Rymazolum), the first compound of the homopyrimidazol series, introduced to therapy as a new minor analgetic, potentiated the analgetic and antagonized the respiratory depressant effect of morphine and its derivatives. In patients with chronic intractable pain, a combination of azidomorphine (0.5 mg) and Probon (150 mg) achieved total pain relief without noticeable euphoria and none of the patients subjected to nalorphine-precipitation showed signs of abstinence according to the Himmelsbach scoring system. Since both the azidomorphines and the homopyrimidazols are unexploited new families, further progress in detail structure-activity relationship studies seems quite promising.

✓ L27 ANSWER 95 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS
AN 77:116428 BIOSIS
TI A PROCEDURE FOR DRUG SCREENING WITHOUT THE NEED TO TRANSPORT URINES

USE OF ION EXCHANGE PAPERS AND HEM AGGLUTINATION INHIBITION.

AU ALEXANDER G J

SO CLIN TOXICOL 9 (3). 1976 435-446. CODEN: CTXAO ISSN: 0009-9309

AB A procedure was devised for screening for drug

abuse in human urine specimens by adsorbing the drugs onto papers loaded with ion-exchange resin. The drugs were then eluted from the papers into aqueous saline buffers, which were analyzed by hemagglutination inhibition with antisera specific for morphine, methadone or barbiturates. The procedure combines the convenience of the ion-exchange papers with the precision and sensitivity of the immunoassay. The preliminary treatment consists of local treatment of urine specimens collected at many distant clinics with ion exchange papers that adsorb 50-65% of alkaloid drugs and 25% of barbiturates and can be shipped, after drying, in simple envelopes by regular mail to a central

analytical laboratory for processing. At the central laboratory, portions of specimens are reconstituted in aqueous saline buffers, while drugs from other portions are extracted with solvents are appropriate pH. Drugs are detected in the reconstituted aqueous media by hemagglutination inhibition and spectrophotofluorimetry and confirmed in the solvent extracts by TLC. Recovery of labeled drugs after this treatment and urine screening data showed that the procedure is safe, convenient and reliable in the case of opiate alkaloids, methadone, amphetamines and phenothiazine tranquilizers but is less suitable for detection of barbiturates.

✓ L27 ANSWER 96 OF 104 MEDLINE
AN 77240457 MEDLINE

TI Possible role of tetrahydroisoquinoline alkaloids in postalcohol intoxication states.
AU Blum K; Eubanks JD; Wallace JE; Schwertner H; Morgan WW
SO Ann N Y Acad Sci, (1976) 273 234-46.
Journal code: 5NM. ISSN: 0077-8923.

✓ L27 ANSWER 97 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS
AN 76:27401 BIOSIS
TI DEVELOPMENTS IN THERAPEUTIC DRUG MONITORING AND ALKALOID ANALYSIS.

AU EVENSON M A
SO FED PROC 34 (12). 1975 2131-2133 CODEN: FEPR77 ISSN: 0014-9446

✓ L27 ANSWER 98 OF 104 MEDLINE
AN 75201763 MEDLINE

TI Interaction of biogenic amines with ethanol.

AU Smith AA
SO Adv Exp Med Biol, (1975) 56 265-75. Ref: 30
Journal code: 2LU. ISSN: 0065-2598.

AB Ethanol through its primary catabolite, acetaldehyde, competitively inhibits oxidation of aldehyde dehydrogenase substrates. As a consequence biogenic amines form increased quantities of alcohols rather than the corresponding acids. During this biotransformation, condensation reactions between deaminated and intact amines may occur which can yield tetrahydropapaverolines. These compounds are closely related to precursors of opioids which is cause to link ethanol abuse to morphine addiction. There is, however, no pharmacological or clinical evidence suggesting similarities between ethanol dependence or opiod addiction. Acetaldehyde plays an additional role in alkaloidal formation in vitro. Biogenic amines may react with acetaldehyde to form isoquinoline or carboline compounds. Some of these substances have significant pharmacological activity. Furthermore, they may enter neural stores and displace the natural neurotransmitter. Thus, they can act as false neurotransmitters. Some investigators believe that chronic ethanol ingestion leads to significant formation of such aberrant compounds which may then upset autonomic nervous system balance. This disturbance may explain the abnormal sympathetic activity seen in withdrawal. While these ideas about the etiology of

alcohol abuse have a definite appeal, they are naturally based on in vitro preliminary work. Much study of the quantitative pharmacology of these compounds in animals is required before judgement can be made as to the merits of the proposed hypotheses. In the meantime, pharmacological studies on the ability of ethanol to depress respiration in the mouse has revealed that unlike opioids or barbiturates, respiratory depression induced by ethanol requires the presence in brain of serotonin. This neurotransmitter also mediates the respiratory effects of several other alcohols but curiously, not chloral hydrate, yet this compound is purported to alter biogenic amine metabolism much like ethanol. Thus, the response to ethanol can be pharmacologically separated from other major narcotic classes such as opioids and barbiturates by respiratory depression effects. The specific requirement for serotonin mediation exhibited by ethanol and several other alcohols opens the door for a rational therapeutic approach to the treatment of alcohol abuse. At the same time, this finding tends to lessen the probability that alcoholism is in some way connected with the formation of addictive alkaloids.

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ANSWER 99 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS

AN 76:199181 BIOSIS

TI CHANGES IN ABSOLUTE AMOUNT OF ALKALOIDS IN DATURA-METEL TREATED WITH CERTAIN GROWTH REGULATORS.

AU GABR A I; ABOU-ZIED E N; SHEDEED M R; EL-SHERBEENY S E

SO HERBA POL 21 (2). 1975 192-200. CODEN: HPBIA9 ISSN: 0018-0599

AB D. metel seedlings were sprayed, or the seeds were soaked before sowing, with solutions of 2-chloroethyl trimethyl ammonium chloride, GA3 or B-9 (N-dimethyl amino-succinamic acid). The treatments caused a decrease or an increase in alkaloid content (measured as hyoscyamine and hyoscyamine) depending on the growth substance, its concentration, method of application, the organ and the age of the plant.

427

ANSWER 100 OF 104 BIOSIS COPYRIGHT 1994 BIOSIS

AN 77:146596 BIOSIS

TI THE DIAGNOSIS AND MANAGEMENT OF ACUTE PSYCHOTIC REACTIONS DUE TO ALCOHOL AND DRUGS.

AU BEAUBRUN M H

SO CARIBB MED J 36 (1). 1975 1-11. CODEN: CMJUA9 ISSN: 0374-7042

AB There are 3 main ways in which drugs may cause or precipitate psychotic states: by intoxication, by producing a psychosis on withdrawal of the drug, and indirectly by the production of anoxia or vitamin deficiencies or by interfering with metabolic processes. Sensory deprivation or isolation can produce a psychosis, and some anesthetic drugs like seryl (1-aryl cyclohexylamine) probably produce their psychotomimetic effects by the sensory deprivation produced. Two major types of psychotic reactions are recognized: the organic confusional states or deliria, and the model psychoses mimicking schizophrenia or mania. These represent a continuum rather than polar opposites. Some drugs like the metallic poisons particularly Pb, stand clearly on the organic

end of the continuum, while hallucinogens like LSD and particularly the analgesic Sernyl are at the other end; there is a wide range of variation in between. The main feature of these 2 types of reaction are described in detail. Reaction to the 4 major chemical groups of true hallucinogens, indole alkaloids, piperidine derivatives, phenylethylamines and cannabinoils are dealt with. The management of psychoses associated with steroid therapy, Antabuse (tetraethylthiuram disulfate) used in treatment of alcoholism, myristicin used in treatment of psychotic illness and anti-depressants, is discussed.

L27 ANSWER 101 OF 104 EMBASE COPYRIGHT 1994 ELSEVIER SCI. B.V.
AN 75164724 EMBASE

TI The biochemical pharmacology of abused

drugs. III. Cannabis, opiates, and synthetic narcotics.

AU Caldwell J.; Sever P.S.

SO CLIN.PHARMACOL.THER., (1974) 16/6 (989-1013).

CODEN: CLPTAT

AB The widely abused plant drug, Cannabis, obtained from the hemp plant Cannabis sativa, and the opiates, from the opium poppy Papaver somniferum, are discussed. The psychoactivity of preparations of these plants has been known for a very long time. Cannabis has never found a genuine medical application for its particular psychoactivity and, although it has been in most of the world's pharmacopoeias at one time or another, there is no established medical use for it. The opiates are essential for the alleviation of severe pain and in the treatment of certain gastrointestinal disorders. Their use in the medicine of the nineteenth century was widespread, but realization of the dangers of prolonged dosage has led to a restriction to circumstances when they are specifically indicated. Owing to the well established dangers of the opiates from the viewpoint of dependence, many attempts have been made to synthesize a 'safe' powerful analgesic. There has been no real success, but several such compounds have come to be abused in their own turn. The three most important of these are meperidine, methadone and pentozocine; these are reviewed along with the naturally occurring opiates.

L27 ANSWER 102 OF 104 MEDLINE

AN 72207752 MEDLINE

TI Narcotic analgesics and antagonists.

AU Lewis JW; Bentley KW; Cowan A

SO Annu Rev Pharmacol, (1971) 11 241-70. Ref: 305

Journal code: 6E3. ISSN: 0066-4251.

L27 ANSWER 103 OF 104 MEDLINE

AN 70000320 MEDLINE

TI Codeine and its alternates for pain and cough relief . 4. Potential alternates for cough relief.

AU Eddy NB; Friebe H; Hahn KJ; Halbach H

SO Bull World Health Organ, (1969) 40 (5) 639-719. Ref: 467

Journal code: C80. ISSN: 0042-9686.

/L27 ANSWER 104 OF 104 MEDLINE
 AN 76192007 MEDLINE
 TI Adverse effects to psychotomimetics. Proposition of a
 psychopharmacological classification. pp. 305-13.
 AU Ban TA
 SO In: Radouco-Thomas S, ed. Pharmacologie, toxicologie, et abus des
 psychotomimetiques (hallucinogenes). Quebec, Les Presses de
 l'Universite Laval, 1974. QV 109 L392p 1973.
 Journal code: IDM. Call number: QV 109 L392p 1973.

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